# CMP-001-011

# A RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROL, PHASE 2/3 STUDY OF FIRST-LINE INTRATUMORAL CMP-001 IN COMBINATION WITH INTRAVENOUS NIVOLUMAB COMPARED TO NIVOLUMAB MONOTHERAPY IN SUBJECTS WITH UNRESECTABLE OR METASTATIC MELANOMA

| | |
|---|---|
| **Study Phase:** | Phase 2/3 |
| **IND Number:** | 16695 |
| **Sponsor:** | Checkmate Pharmaceuticals, Inc.<br>245 Main Street, 2nd Floor<br>Cambridge, MA 02142 USA |
| **Issue Date:** | Original Protocol 11 September 2020<br>Amendment 1 (Version 2.0) 04 February 2021 |

# INVESTIGATOR'S AGREEMENT

**A RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROL, PHASE 2/3 STUDY OF FIRST-LINE INTRATUMORAL CMP-001 IN COMBINATION WITH INTRAVENOUS NIVOLUMAB COMPARED TO NIVOLUMAB MONOTHERAPY IN SUBJECTS WITH UNRESECTABLE OR METASTATIC MELANOMA**

**Protocol Number: CMP-001-011**

I have read this protocol and agree to the following:

- I am thoroughly familiar with the appropriate use of the investigational drug, as described in this protocol, and any other information provided by the Sponsor including, but not limited to, the current Investigator's Brochure provided by the Sponsor.
- I will conduct the study in compliance with this protocol, with any future amendments, and with any other written study conduct procedures provided and reviewed and approved by the Sponsor or its representatives.
- I will conduct the study in accordance with the current US Food and Drug Administration (FDA)/applicable local regulations, International Conference on Harmonization (ICH) guidelines, and any other applicable regulatory requirements as well as Good Clinical Practice (GCP) standards (CPMP/ICH/135/95); the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the principles of GCP; and all local ethical and legal requirements and will complete the study within the time designated.
- I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the drug and the conduct of the study.
- I agree that the Sponsor or its representatives shall have access to any source documents from which electronic case report form (eCRF) information may have been generated.

_____

Printed Name of Investigator

_____ _____

Signature of Investigator Date

# SPONSOR PROTOCOL APPROVAL

I have read this protocol and approve the design of this study:

[redacted]

Checkmate Phannaceuticals, Inc.

[redacted]

# PROCEDURES IN CASE OF EMERGENCY

**Emergency Contact Information**

| Name | Role in Study | Address and Telephone Number |
|---|---|---|
| Checkmate Pharmaceuticals, Inc. | Sponsor | 245 Main Street, 2nd Floor<br>Cambridge, MA, 02142 USA<br>Phone: 617-682-3625 |
| IQVIA Biotech | Medical Monitor<br>24-Hour emergency contact | IQVIA Biotech<br>Email: CMP-001-011@novellaclinical.com |

Serious adverse events (SAEs) should be recorded on the SAE Report Form and completed and submitted to IQVIA Biotech Safety preferably via email to: **Safety-Inbox.Biotech@IQVIA.com** or by fax to **+1-866-761-1274** as back up within 24 hours of awareness.

# SYNOPSIS

**Name of Sponsor/Company:** Checkmate Pharmaceuticals, Inc.

**Study Drugs:**

- CMP-001 in combination with nivolumab (OPDIVO®)
- Nivolumab monotherapy

**Title of Study:** A Randomized, Open-Label, Active-Control, Phase 2/3 Study of First-Line Intratumoral CMP-001 in Combination with Intravenous Nivolumab Compared to Nivolumab Monotherapy in Subjects with Unresectable or Metastatic Melanoma

**Study Center(s):** Enrollment is anticipated at clinical sites in regions including (but not limited to) North America, Europe, and Asia Pacific

**Phase of Development:** Phase 2/3

**Study Objectives:**

**Phase 2 Objectives:**

Phase 2 Primary Objective

- To determine confirmed objective response rate (ORR) for treatment with first-line CMP-001 in combination with nivolumab versus nivolumab monotherapy in subjects with unresectable or metastatic melanoma

Phase 2 Secondary Objective

- To evaluate the safety and tolerability of first-line CMP-001 in combination with nivolumab versus nivolumab monotherapy in subjects with unresectable or metastatic melanoma

**Phase 3 Objectives:**

Phase 3 Primary Objective

- To evaluate progression-free survival (PFS) for subjects receiving first-line CMP-001 in combination with nivolumab versus nivolumab monotherapy for unresectable or metastatic melanoma

Phase 3 Secondary Objectives

- To evaluate the safety and tolerability of first-line CMP-001 in combination with nivolumab versus nivolumab monotherapy in subjects with unresectable or metastatic melanoma
- To evaluate the efficacy of first-line CMP-001 in combination with nivolumab versus nivolumab monotherapy in subjects with unresectable or metastatic melanoma

Phase 3 Exploratory Objectives

- To evaluate the effect of first-line CMP-001 in combination with nivolumab on injected and non-injected target lesions in subjects with unresectable or metastatic melanoma
- To evaluate the pharmacodynamic effects of first-line CMP-001 in combination with nivolumab in subjects with unresectable or metastatic melanoma

**Study Endpoints:**

**Phase 2 Endpoints**

Phase 2 Primary Endpoint

ORR defined as the proportion of subjects with a confirmed objective response of complete response (CR) or partial response (PR) based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) as determined by Blinded Independent Central Review (BICR)

Phase 2 Secondary Endpoint

Adverse events (AEs), serious adverse events (SAEs), and AEs leading to discontinuation or death and severity of AEs as assessed by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0

**Phase 3 Endpoints:**

Phase 3 Primary Endpoint:

Progression-free survival (PFS) defined as the time from the date of randomization to first date of documented progressive disease based on RECIST v1.1 by BICR or death from any cause, whichever occurs first

Phase 3 Secondary Endpoints:

- AEs, SAEs, and AEs leading to discontinuation or death, and severity of AEs as assessed by NCI CTCAE v5.0
- Overall survival (OS), defined as the time from the date of randomization until death from any cause
- Confirmed ORR defined as the proportion of subjects with a confirmed objective response of CR or PR based on RECIST v1.1 as determined by BICR
- Duration of response (DOR) defined as the time from date of first documented response (CR or PR) to date of documented progressive disease, based on RECIST v1.1 as determined by BICR
- Disease control rate (DCR), defined as the proportion of subjects who have a confirmed best response of CR or PR, or stable disease lasting at least 4 months, based on RECIST v1.1 as determined by BICR
- Treatment response in non-injected target lesions based on RECIST v1.1 by Investigator
- PFS, ORR, DOR, and DCR based on RECIST v1.1, and immune PFS, immune DOR, and immune ORR based on immunotherapy RECIST (iRECIST) as determined by Investigator assessment

**Exploratory Endpoints:**

- [redacted]
- Change from Baseline in blood concentrations of C-X-C motif chemokine 10 (CXCL10) after treatment with CMP-001
- Baseline, and change from Baseline, in tumor or blood measurements of biomarkers related to toll-like receptor 9 (data from Phase 2 portion of the study)

**Methodology:**

This is a randomized, open-label, active-control study of first-line CMP-001 administered by intratumoral (IT) injection in combination with intravenous (IV) nivolumab versus nivolumab monotherapy in subjects with Stage III or IV unresectable or metastatic melanoma who have not been previously treated with a programmed cell death protein 1 (PD-1) blocking antibody for metastatic disease.

The study will follow a Phase 2/3 design. The study will enroll eligible subjects into the Phase 2 portion of the study; enrollment into the Phase 3 portion of the study will not proceed until the primary endpoint of Phase 2 is evaluated.

The Phase 2 primary endpoint of ORR per RECIST v1.1 by BICR will be assessed approximately 30 weeks after the last subject is randomized into the Phase 2 portion of the study. If the primary endpoint of Phase 2 is met, subjects enrolled in the Phase 2 portion of the study will continue to receive study treatment (in Arm A or Arm B) in the Phase 3 portion of the study, and enrollment will proceed in Phase 3. If the Phase 2 primary endpoint is not met, subjects enrolled in Phase 2 may remain in the study and continue to receive study treatment until a reason for treatment discontinuation is met but no further subjects will be enrolled.

An Independent Data Monitoring Committee will review safety and efficacy data throughout the study.

**Number of Subjects (Planned):**

A total of 450 subjects will be randomized into this Phase 2/3 study, including 140 subjects randomized into the Phase 2 portion and 310 subjects randomized into the Phase 3 portion of the study. Subjects will be randomized in a 1:1 ratio to either:

- Arm A: CMP-001 in combination with nivolumab
- Arm B: nivolumab monotherapy

During the randomization process, treatment groups will be stratified based on:

- TNM Stage American Joint Committee on Cancer (AJCC) Cancer Staging Manual Eighth Edition (M0/M1a/M1b versus M1c/M1d)
- Tumor PD-L1 expression (≥5% versus <5%)

**Diagnosis and Main Criteria for Inclusion:**

**Inclusion Criteria:**

Subjects enrolled in the study must meet all of the following inclusion criteria to be eligible:

1. Histologically or cytologically confirmed unresectable Stage III or Stage IV melanoma per AJCC Cancer Staging Manual Eighth Edition.
2. Measurable disease, as defined by RECIST v1.1 and both of the following:
   a. At least 1 accessible lesion amenable to repeated IT injection
   b. One or more measurable lesions at least 1 cm in diameter that are not intended for CMP-001 injection and can be followed as target lesions per RECIST v1.1
3. Able to provide tissue from a core or excisional/incisional biopsy (fine needle aspirate is not sufficient). A newly obtained biopsy (within 90 days before the first dose of study treatment) is mandatory, but an archival sample is acceptable if no intervening therapy for melanoma/cancer was received.

   Note: for tissue sampling details, please refer to the Laboratory Manual.

4. Adequate organ function based on most recent laboratory values within 3 weeks before the first dose of study treatment on Week 1 Day 1 (W1D1):
    a. Bone marrow function:
        – neutrophil count ≥1500/mm$^3$
        – platelet count ≥ 100 000/mm$^3$
        – hemoglobin concentration ≥9 g/dL
        – white blood cells ≥2000/mm$^3$
    b. Liver function:
        – total bilirubin ≤1.5 × the upper limit of normal (ULN) with the following exception: subjects with Gilbert Disease total serum bilirubin ≤3 × ULN
        – aspartate aminotransferase and alanine aminotransferase ≤3 ×ULN
    c. Lactate dehydrogenase ≤2 × ULN
    d. Renal function: estimated (Cockcroft-Gault) or measured creatinine clearance ≥30 mL/min
    e. Coagulation
        – International normalized ratio or prothrombin time (PT) ≤ 1.5 × ULN, unless subject is receiving anticoagulant therapy, as long as PT or partial thromboplastin time (PTT) is within therapeutic range of intended use of anticoagulants
        – Activated partial thromboplastin time or PTT ≤1.5 × ULN, unless subject is receiving anticoagulant therapy, as long as PT or PTT is within therapeutic range of intended use of anticoagulants
5. Eastern Cooperative Oncology Group Performance Status of 0 to 1 at Screening.
6. Age ≥18 years at time of consent.
7. Capable of understanding and complying with protocol requirements.
8. Women of childbearing potential must have negative serum pregnancy test prior to dosing at W1D1 and be willing to use an adequate method of contraception (Section 4.3.2) from the time of consent until at least 150 days after the last dose of study treatment.
9. Able and willing to provide written informed consent and to follow study instructions. Subjects unable to provide written informed consent on their own behalf will not be eligible for the study.

**Exclusion Criteria:**

Subjects presenting with any of the following will not qualify for entry into the study:

1. Uveal, acral, or mucosal melanoma.
2. Received prior systemic treatment for melanoma in the unresectable or metastatic setting. Prior adjuvant therapy is acceptable if the treatment course (of approximately 1 year duration) was completed and there was no recurrence within 6 months of the last dose of adjuvant treatment.
3. Received prior therapy with CMP-001.

4. Requires systemic pharmacologic doses of corticosteroids greater than the equivalent of 10 mg/day prednisone within 30 days before the first dose of study treatment on W1D1.
    a. Subjects who are currently receiving steroids at a prednisone-equivalent dose of ≤10 mg/day do not need to discontinue steroids prior to enrollment.
    b. Replacement doses, topical, ophthalmologic, and inhalational steroids are permitted.
5. History of CTCAE v5.0 Grade 4 immune-related AE due to adjuvant CTLA-4 or PD-1 blocking antibody.
6. Not fully recovered from adverse events (to Grade 1 or less [per CTCAE v5.0], with the exception of persistent alopecia, adrenal insufficiency, and hypothyroidism) due to prior treatment.
7. Active pneumonitis, history of pneumonitis that required steroids, or history of interstitial lung disease.
8. Severe uncontrolled cardiac disease within 6 months of Screening, including but not limited to poorly controlled hypertension, unstable angina, myocardial infarction, congestive heart failure (New York Heart Association Class II or greater), pericarditis within the previous 6 months, cerebrovascular accident, and implanted or continuous use of a pacemaker or defibrillator.
9. Known history of immunodeficiency.
10. Known additional malignancy that has progressed or required active treatment within the past 3 years. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, curatively treated localized prostate cancer with prostate-specific antigen level below 4.0 ng/mL, in situ cervical cancer on biopsy or a squamous intraepithelial lesion on Papanicolaou smear, thyroid cancer (except anaplastic), and adjuvant hormonal therapy for breast cancer >3 years from curative-intent surgical resection.
11. Active autoimmune disease that has required systemic treatment in past 2 years; replacement therapy is not considered a form of systemic treatment.
12. Untreated, symptomatic, or enlarging central nervous system metastases or carcinomatous meningitis (including leptomeningeal metastases from solid tumors).
13. Prior allogenic tissue/solid organ transplant.
14. Known or suspected active infection with severe acute respiratory syndrome coronavirus 2 virus (SARS-CoV-2).
15. Active infection requiring systemic therapy.
16. Known or suspected infection with HIV, hepatitis B virus, or hepatitis C virus; testing is not required unless suspected.
17. Received a live/attenuated virus vaccination within 30 days prior to the first dose of study treatment on W1D1.
18. Received blood products (including platelets or red blood cells) or colony stimulating factors (including granulocyte colony stimulating factor, granulocyte/macrophage colony stimulating factor, or recombinant erythropoietin) within 30 days prior to the start of Screening.
19. History of permanent discontinuation of nivolumab due to infusion reactions.

20. Any concurrent uncontrolled illness, including mental illness or substance abuse, which in the opinion of the Investigator, would make the subject unable to cooperate or participate in the trial.
21. Participation in another clinical study of an investigational anticancer therapy or device within 30 days before the first dose of study treatment on W1D1.

    Note: Participation in the follow-up phase (receiving no study treatment) of a prior study is allowed.
22. Requires prohibited treatment (ie, non-protocol specified anticancer pharmacotherapy, surgery, or radiotherapy) for treatment of malignant tumor.
23. Has a life expectancy of less than 3 months and/or has rapidly progressing disease (eg, tumor bleeding, uncontrolled tumor pain) in the opinion of the treating Investigator.
24. Pregnant or breast-feeding or expecting to conceive or donate eggs within the projected duration of the study, from the time of consent until at least 150 days after the last dose of study treatment for women.

**Investigational Study Drug, Dosage, and Mode of Administration:**

Subjects assigned to Arm A will receive CMP-001 10 mg weekly for 7 doses (W1D1 to W7D1), after which CMP-001 10 mg IT will be administered every 3 weeks (Q3W) until a reason for treatment discontinuation is reached. A prophylaxis regimen is required before each dose of CMP-001. The first dose of CMP-001 may be administered subcutaneously (SC) or by IT injection at the discretion of the Investigator; all subsequent doses are planned to be administered by IT injection. The initial 7 CMP-001 weekly dose schedule must be completed before starting the Q3W CMP-001 dosing schedule.

Subjects in Arm A and Arm B will receive nivolumab 360 mg IV over 30 minutes at W1D1 and Q3W thereafter until the subject satisfies a condition for study treatment discontinuation. Please refer to the nivolumab Investigator's Brochure.

On visits where CMP-001 and nivolumab are both administered, CMP-001 should always be administered before nivolumab.

**Duration of Treatment:**

Subjects will receive study treatment until they reach a reason for treatment or study discontinuation (Section 4.5 and Section 4.6). Subjects may continue study treatment beyond disease progression based upon Investigator judgement of potential benefit.

If a subject achieves and maintains a confirmed CR or iCR by Investigator assessment, IT or SC injections of CMP-001 or the combination of CMP-001 and nivolumab may be discontinued at the Investigator's discretion once the subject meets both of the following criteria:

- Subject has been treated for at least 48 weeks (the maximum duration of study treatment is 2 years)
- Subject has received at least 3 doses of assigned treatment beyond the date of the initial CR/iCR

Subjects who discontinue study treatment should complete the end of treatment visit and 100-day safety follow-up. Subjects who are post-treatment but have not met criteria for study discontinuation should remain on study for post-treatment follow-up and long-term survival

follow-up and receive study evaluations for efficacy according to the Schedule of Assessments (Table 1).

Subjects who permanently discontinue (for >12 weeks) CMP-001 or nivolumab may not be re-treated with the discontinued study treatment in this study. When nivolumab is permanently discontinued due to an immune related AE, CMP-001 must also be permanently discontinued.

**Criteria for Evaluation:**

**Efficacy:**

Disease status will be assessed by computed tomography or magnetic resonance imaging and other appropriate measures according to the Schedule of Assessments (Table 1). Calipers and photographs containing a ruler may be used to facilitate measurement of superficial cutaneous tumors. Objective responses will be assessed by BICR and the Investigator according to RECIST v1.1. Subjects who continue study treatment beyond PD according to RECIST v1.1 will be assessed by the Investigator according to iRECIST. Other endpoints in Phase 3 include PFS, DCR, and DOR.

**Safety:**

Safety and tolerability will be assessed by evaluating the following:

- Treatment-emergent adverse events, which will be evaluated and assigned a grade using CTCAE v5.0
- Vital signs (oral temperature, respiratory rate, pulse, and systolic and diastolic blood pressure), and physical examination (including weight and body mass index)
- Clinical laboratory assessments (chemistry, hematology, urinalysis, coagulation, and thyroid function tests)
- 12-lead electrocardiograms (ECGs)

**Statistical Methods:**

**Sample Size:**

A total of 450 subjects will be randomized in this Phase 2/3 study.

In the Phase 2 portion of the study, a total of 140 subjects will be randomized in a 1:1 ratio to the 2 treatment arms to receive CMP-001 in combination with nivolumab or nivolumab monotherapy. The sample size is calculated to compare the ORR between the 2 treatment arms. A sample size of 140 provides 80% power to detect an absolute treatment difference of 25% with 2-sided alpha level of 0.05, assuming that the ORR in CMP-001 in combination with nivolumab is 65% and the ORR in nivolumab monotherapy is 40%.

If the treatment effect on ORR at end of the Phase 2 portion of the study is statistically significant at a 2-sided alpha level of 0.05, an additional 310 subjects may be randomized in a 1:1 ratio to receive CMP-001 in combination with nivolumab or nivolumab monotherapy. In combination with the 140 subjects randomized in Phase 2, this will make up the Phase 3 study population of 450 subjects.

The overall study sample size (n=450) is calculated to compare the PFS between the 2 treatment arms at an alpha level of 0.05 (2-sided). The final PFS analysis will be performed when at least 331 BICR PFS events have been observed across the 2 treatment arms. With 331 PFS events, the study has 90% power to demonstrate treatment effect in PFS at 0.05 alpha level (2-sided) when the true hazard ratio (HR) is 0.70. The smallest treatment effect that can be detected statistically significant in this study is HR 0.805.

**Statistical Analysis Methods:**

Study analysis sets for safety and efficacy will include:

- Intent-to-Treat Analysis Set: all subjects who are randomized
- Safety Analysis Set: all subjects who receive at least 1 dose of study treatment
- Per Protocol Analysis Set: all subjects who are randomized and are without major protocol deviations
- Pharmacodynamic Analysis Set: all subjects who receive at least 1 dose of CMP-001 and have at least 1 measurable sample at Baseline and at least 1 evaluable biomarker sample after CMP-001 administration

The Phase 2 analysis sets apply to subjects who were randomized or treated in the Phase 2 portion. The Phase 3 analysis sets apply to all subjects who were randomized or treated in both Phase 2 and Phase 3 portions.

The Phase 2 primary endpoint, ORR, will be analyzed using a 2-sided Cochran-Mantel-Haenszel test stratified by stage and PD-L1 expression to compare the 2 treatment arms. Associated odds ratio and 95% CI will also be calculated. Additionally, ORR and the 95% exact CIs will be calculated using the Clopper-Pearson method for each of the 2 treatment arms. The secondary endpoint DCR and the 95% Clopper-Pearson CIs will be summarized as well.

The Phase 3 primary endpoint, PFS, will be analyzed using a 2-sided log-rank test stratified by stage and PD-L1 expression to compare the 2 treatment arms. Subject data from the Phase 2 and Phase 3 portions will be combined to create the full study sample for all Phase 3 analyses. HRs and corresponding 2-sided 95% CIs will be estimated using a Cox proportional hazards model, with treatment arm as a single covariate, stratified by the above factors. PFS curves, PFS medians with 95% CIs, and PFS rates at 6 and 12 months with 95% CIs will be estimated using Kaplan-Meier methodology. The secondary endpoints OS and DOR will be analyzed using the same approach as PFS.

Safety data, including vital signs, ECGs, laboratory test results, physical examinations, and AEs, will be summarized by assessment time points, as appropriate. Change from Baseline will be included in summary tables for laboratory, ECG, and vital sign parameters.

**Table 1: Schedule of Assessments**

| Procedure or Assessment | Screening (Day -30 to Day -1) | W1D1 | W2D1 | W3D1 | W4D1 | W5D1 | W6D1 | W6D2 | W7D1 | Q3W (W10, W13, etc) | End of Treatment (EOT)[a] | 100-Day Follow-up (100DFU)[b] | Post-treatment Follow-up (PTFU)[c] (Q3mo) | Long-Term Survival Follow-up (LTSFU)[d] (Q3mo) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Windows** | **N/A** | **N/A** | **±2 d** | **±2 d** | **±2 d** | **±2d** | **±2 d** | **N/A** | **±2 d** | **±3 d** | **+7 d** | **+7 d** | **± 2 weeks** | **± 4 weeks** |
| CMP-001 Injection (Dose Number)[e] | | 1 SC/IT | 2 | 3 | 4 | 5 | 6 | | 7 | 8+ | | | | |
| Nivolumab Dosing (Dose Number)[f] | | 1 | | | 2 | | | | 3 | 4+ | | | | |
| Informed Consent | X | | | | | | | | | | | | | |
| Eligibility Criteria Assessment | X | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | |
| Melanoma History | X | | | | | | | | | | | | | |
| Prior Cancer Treatment | X | | | | | | | | | | | | | |
| Physical Examination[g] | X | X | | X | | | | | X | X | X | | | |
| Vital Signs[h] | X | X | X | X | X | X | X | X | X | X | X | | | |
| ECOG Performance Status | X | X | | X | | | | | X | X | X | | | |
| Adverse Event Monitoring[i] | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Concomitant Medications[j] | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| 12-Lead ECG[k] | X | X | | X | | | | | X | | X | | | |
| Clinical Laboratory Tests (hematology, serum chemistry, urinalysis)[l] | X | X | X | X | X | X | X | | X | X | X | | | |
| Coagulation Tests[l] | | X | | | | | | | X | X | X | | | |
| Thyroid Function Tests[l] | X | | | X | | | | | X | X | X | | | |

**Table 1: Schedule of Assessments (Continued)**

| Procedure or Assessment | Screening (Day -30 to Day -1) | W1D1 | W2D1 | W3D1 | W4D1 | W5D1 | W6D1 | W6D2 | W7D1 | Q3W (W10, W13, etc) | End of Treatment (EOT)[a] | 100-Day Follow-up (100DFU)[b] | Post-treatment Follow-up (PTFU)[e] (Q3mo) | Long-Term Survival Follow-up (LTSFU)[f] (Q3mo) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Windows** | **N/A** | **N/A** | **±2 d** | **±2 d** | **±2 d** | **±2 d** | **±2 d** | **N/A** | **±2 d** | **±3 d** | **+7 d** | **+7 d** | **± 2 weeks** | **± 4 weeks** |
| CMP-001 Injection (Dose Number)[e] | | 1 SC/IT | 2 | 3 | 4 | 5 | 6 | | 7 | 8+ | | | | |
| Nivolumab Dosing (Dose Number)[f] | | 1 | | | 2 | | | | 3 | 4+ | | | | |
| Autoimmune Laboratory Panel[l] | X | | | | | | | | X | | X | | | |
| Pregnancy Test and Follicle Stimulating Hormone[l] | X | X | | | X | | | | X | X | X | | | |
| Exploratory Biomarker Sampling[m] | | X | | | | X | X | X | X | | | | | |
| Tumor Biopsy (PD-L1 status)[n] | X | | | | | X | | | | | | | | |
| Disease Assessment (radiographic imaging)[o] | [redacted] | | | | | | | | | | | | | |
| Disease Assessment (CNS Imaging)[o] | | | | | | | | | | | | | | |
| Disease Assessment (photographic imaging)[o] | | | | | | | | | | | | | | |
| 100-Day Follow-up (Office or Phone Call) | | | | | | | | | | | | X | | |
| Long-Term Survival Follow Up Phone Call | | | | | | | | | | | | | | X |

Abbreviations: 100DFU = 100-day follow-up; AE= adverse event; CNS = central nervous system; CR = complete response; CT = computed tomography; D/d = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = End Of Treatment; FSH = follicle stimulating hormone; iRECIST = immunotherapy Response Evaluation Criteria in Solid Tumors; iCR = immune complete response; INR = international normalized ratio; iPR = immune partial response; IT = intratumoral; LTSFU = Long-Term Survival Follow-up; MRI = magnetic resonance imaging; N/A = not applicable; PD-L1 = programmed cell death protein ligand 1; PET = positron emission tomography; PR = partial response; PT = prothrombin time; PTFU = Post-treatment Follow-up; PTT = partial thromboplastin time; RECIST = Response Evaluation Criteria in Solid Tumors; Q3mo = every 3 months; Q3W = every 3 weeks; Q6W = every 6 weeks; SC = subcutaneous; SAE = serious adverse event; W = week; WOCBP = women of child bearing potential.

a. End of Treatment assessments to be performed within 7 days following subject discontinuation from the last study treatment (either CMP-001 or nivolumab). Removal of a subject from CMP-001 treatment is defined as the time in which the Investigator decides to discontinue study treatment. If a subject has CMP-001 dosing withheld for more than 3 consecutive doses for any reason during the Q3W dosing period, resumption of treatment must be discussed with the Medical Monitor, otherwise, the subject will be discontinued from study treatment and will have all EOT assessments performed.
b. The 100DFU is a safety follow-up visit that may be conducted at the study site or via phone. This visit should occur 100 days (+7) after the EOT.
c. Post-treatment Follow-up (PTFU) will be conducted every 3 months (± 2 weeks) for all subjects who discontinue study treatment but have not met criteria for study discontinuation. These subjects should remain on study and receive disease assessments every 3 months, until discontinuation.
d. Long-Term Survival Follow-up (LTSFU) will be conducted every 3 months (± 4 weeks) after the EOT visit or the last disease assessment date in PTFU and may occur via phone.
e. CMP-001 dosing will begin on W1D1. Weekly dosing: A window of ±2 days is permitted for CMP-001 dosing from W2D1 to W7D1. The first dose of CMP-001 may be administered SC or IT, at the discretion of the Investigator; all subsequent doses are planned to be administered IT until no injectable lesions remain. Subjects must complete all 7 weekly CMP-001 doses before moving to the Q3W dosing schedule. Q3W dosing (W10D1+): A window of ±3 days is permitted for CMP-001 dosing from W10D1 throughout the trial. When nivolumab is permanently discontinued due to an immune related AE, CMP-001 must also be permanently discontinued. Refer to Section 5.3 for Treatment Compliance.
f. Nivolumab dosing will begin on W1D1 and continue Q3W throughout the study for a maximum of 2 years. For subjects in Arm A, when CMP-001 injection and nivolumab dosing fall on the same day, CMP-001 injection will be given before nivolumab dosing. Refer to Section 5.1.1 for Nivolumab Dosing.
g. A full physical examination (PE) will be conducted at Screening and EOT. If the Screening full PE is performed >72 hours before the W1D1 visit, then a brief (symptom directed) PE must be performed within 72 hours before the first injection of CMP-001. Brief PEs focused on areas of disease or AEs must be performed at the W1D1, W3D1, W7D1 CMP-001 injection visits, at every CMP-001 injection visit thereafter, and at any other time as clinically indicated. Height will be obtained at Screening only and weight will be obtained at all PE assessments.
h. Vital signs include measurement of blood pressure (systolic and diastolic blood pressure), respiratory rate, heart rate, and body temperature. Blood pressure and heart rate should be taken in the seated position following ≥3 minutes of rest. For subjects in Arm A, for the first 6 CMP-001 dosing visits (W1D1 to W6D1), vital signs must be collected prior to the CMP-001 injection and at 30-minute (±15 minutes) intervals for 4 hours after CMP-001 injection. Starting at W7D1, observation periods may be reduced to a minimum of 1 hour following CMP-001 injection at the Investigator's discretion based on the AE profile of the individual subject. When vital signs are scheduled at the same time as collection of a blood sample, the vital sign measurements should be obtained before the scheduled phlebotomy. If a study visit occurs where only nivolumab is administered, vital signs must be collected before the start of the nivolumab infusion.
i. AEs will be assessed continually from the time of informed consent through 100 days after the last dose of study treatment or until an alternative cancer treatment is initiated, whichever occurs first, for all subjects. Subjects who discontinue CMP-001 but remain on treatment with nivolumab will continue to have AEs collected according to this schedule until 100 days after the last dose of nivolumab.
j. Concomitant medications will be assessed continually from 30 days before the first dose of study treatment through 100 days after the last dose of study treatment or until an alternative cancer treatment is initiated, whichever occurs first. Treatment medications for AEs related to study treatment that occur more than 100 days after the last dose of study treatment will be collected.
k. 12-lead ECGs will be obtained at Screening, before the W1D1, W3D1, and W7D1 CMP-001 injections, and at EOT. ECG parameters will include heart rate and PR, QRS, QT, and QT corrected for heart rate (using Fridericia's formula) intervals. ECGs will be performed after the subject has been resting in supine or semi-supine position for at least 5 minutes. When an ECG is scheduled at the same time as a blood sampling, the ECG reading should be obtained before the scheduled blood sampling.
l. Clinical laboratory assessments may be performed up to 72 hours before the study treatment administration. When clinical laboratory assessments are done the same day as study treatment administration, vital signs should be performed prior to collection of clinical laboratory tests; an extension up to 72 hours prior to the start of study treatment is permissible in situations where results cannot be obtained within the standard 24-hour window. Refer to Section 7.1.12 for Clinical Laboratory Assessments.
Note: For WOCBP a serum pregnancy test should be done at Screening. Serum **or** urine pregnancy tests should be done prior to the first CMP-001 injection on W1D1, W4D1, W7D1, Q3W thereafter, and EOT. An FSH test is required at screening to confirm menopause (FSH level >40 mIU/mL) in women <55 years of age (Section 4.3.1). Refer to Section 7.1.13 for Pregnancy Testing.
Note: Coagulation samples (PT, INR, and PTT) to be collected and results reviewed prior to the W1D1 CMP-001 injection visit and prior to every CMP-001 injection beginning at W7D1 and continuing Q3W thereafter.
m. Exploratory biomarker blood samples are to be collected at the following time points during the Phase 2 portion of the study only: W1D1 within 2 hours before CMP-001 injection; W5D1 (same day as tumor biopsy) before CMP-001 injection; W6D1 within 2 hours before CMP-001 injection, 4 hours (± 30 minutes) after CMP-001 injection, and 24 hours (± 4 hours) after CMP-001 injection (W6D2); and W7D1 within 2 hours before CMP-001 injection. Refer to Section 7.3.1 Collection of Blood for Translational Biomarker Analyses.
n. Fresh tumor biopsy samples are mandatory, if safe and medically feasible, at Screening (before W1D1) and W5D1 (±1 week) prior to CMP-001 IT injection. If the Investigator believes it is unsafe to perform a biopsy, the subject may be considered eligible after discussion with the Medical Monitor if tissue and/or prior assessments are available to determine PD-L1 expression. Archival tumor biopsy samples should also be collected during Screening, if available. Refer to Section 7.3.2 for Tumor Biopsies.
o. Disease Assessment methods include radiographic (contrast-enhanced CT alone or in combination with PET or MRI), photographic, and CNS imaging by contrast-enhanced CT or MRI (per site local standards). The same modality used at Screening must be used throughout the study. Disease assessments will be performed predose beginning at W10D1 (-7 days) and repeated every 6 weeks (-7 days) (eg, W16D1, W22D1, etc). A response (CR, PR, iCR or iPR [per RECIST v1.1 or iRECIST]) will be confirmed with follow-up disease assessments performed at least 4 weeks after the date of initial response. Disease assessments will continue every 6 weeks after the confirmatory scans. All scans should be performed at least 2 weeks after a previous CMP-001 IT injection to prevent injection-related pseudoprogression. Disease assessments will be performed every 12 weeks for subjects continuing on study more than 1 year. Refer to Section 7.2 for Disease Assessments.
p. Baseline CNS imaging by contrast-enhanced CT or MRI must be provided at Screening; on-study CNS imaging is required only if symptoms or history of CNS disease is present at Baseline.

# TABLE OF CONTENTS

# LIST OF TABLES

# LIST OF FIGURES

# LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation or Specialist Term | Explanation |
|---|---|
| ADL | activities of daily living |
| AE | adverse event |
| AJCC | American Joint Committee on Cancer |
| AST | aspartate aminotransferase |
| ATC | Anatomical Therapeutic Chemical |
| BICR | Blinded Independent Central Review |
| BOR | best overall response |
| $C_{avg28}$ | average serum concentration at Day 28 |
| CD | cluster of differentiation |
| CFR | Code of Federal Regulations |
| cHL | classical Hodgkin lymphoma |
| CL | clearance |
| $CL_{ss}$ | steady state clearance |
| $C_{min28}$ | trough serum concentration at Day 28 |
| CNS | central nervous system |
| CpG | cytosine linked to a guanine by a phosphate bond |
| CR | complete response |
| CRA | Clinical Research Associate |
| CRC | colorectal cancer |
| CT | computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTL | cytotoxic T lymphocyte |
| CTLA-4 | cytotoxic T-lymphocyte-associated protein 4 |
| CV | coefficient of variation |
| CXCL10 | C-X-C motif chemokine 10 |
| DCR | disease control rate |
| DOR | duration of response |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| eGFR | estimated glomerular filtration rate |
| EOT | end of treatment |
| ER | exposure response |

| Abbreviation or Specialist Term | Explanation |
|---|---|
| FDA | Food and Drug Administration |
| FSH | follicle stimulating hormone |
| GCP | Good Clinical Practice |
| HCC | hepatocellular carcinoma |
| HR | hazard ratio |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonisation |
| iCR | immune complete response |
| ID | identification |
| IDMC | Independent Data Monitoring Committee |
| iDOR | immune duration of response |
| IEC | Independent Ethics Committee |
| IFN | interferon |
| IMAE | immune-mediated adverse event |
| INR | international normalized ratio |
| iORR | immune objective response rate |
| iPFS | immune progression-free survival |
| iPR | immune partial response |
| IRB | Institutional Review Board |
| iRECIST | immunotherapy Response Evaluation Criteria in Solid Tumors |
| iSD | immune stable disease |
| IT | intratumoral(ly) |
| itRECIST | intratumoral Response Evaluation Criteria in Solid Tumors |
| ITT | Intent-to-Treat |
| iUPD | immune unconfirmed progressive disease |
| IV | intravenous |
| IWRS | Interactive Web Response System |
| LTSFU | long-term survival follow-up |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MEK | mitogen-activated protein kinase |
| MRI | magnetic resonance imaging |
| NCI | National Cancer Institute |
| NSCLC | non-small cell lung cancer |
| ODN | oligodeoxynucleotide |

| Abbreviation or Specialist Term | Explanation |
|---|---|
| ORR | objective response rate |
| OS | overall survival |
| PD | progressive disease |
| PD-1 | programmed cell death protein 1 |
| pDC | plasmacytoid dendritic cell |
| PD-L1 | programmed death-ligand 1 |
| PET | positron emission tomography |
| PFS | progression-free survival |
| PK | pharmacokinetics |
| PPK | population pharmacokinetics |
| PR | partial response |
| PS20 | polysorbate 20 |
| PT | prothrombin time |
| PTFU | Post-treatment Follow-up |
| PTT | partial thromboplastin time |
| Q2W | every 2 weeks |
| Q3W | every 3 weeks |
| Q4W | every 4 weeks |
| Qb | Qbeta |
| QTc | QT corrected |
| RCC | renal cell carcinoma |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RVT | residual viable tumor |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SC | subcutaneous (ly) |
| SCCHN | squamous cell carcinoma of the head and neck |
| SD | stable disease |
| SOC | system organ class |
| SOP | standard operating procedure |
| TB | total bilirubin |
| TEAE | treatment-emergent adverse event |
| TLR9 | toll-like receptor 9 |
| ULN | upper limit of normal |
| USPI | United States Prescribing Information |

| Abbreviation or Specialist Term | Explanation |
|---|---|
| VLP | virus-like particle |
| WNL | within normal limits |

# 1. INTRODUCTION

## 1.1. Background

Melanoma remains the most common cause of skin cancer death in the United States, Europe, and Australia. Despite an evolving understanding of the molecular aberrations and clinical factors that impact outcomes as well as improvements in the therapeutic paradigm, including immunotherapy, metastatic melanoma remains essentially incurable in view of the limited efficacy and the toxicity of the currently available agents. Over the past 10 years, newly approved treatment options with programmed cell death protein 1 (PD-1) blocking antibodies have improved survival outcomes in patients with melanoma, including patients with previously treated unresectable melanoma or treatment-naïve advanced melanoma. Treatment with a single-agent PD-1 blocking antibody resulted in objective response rates (ORR) of 34% to 40%, median progression-free survival (PFS) ranging from 4.1 to 6.9 months, and long-term (5-year) survival rates up to 45% (KEYTRUDA® United States Prescribing Information [USPI]; OPDIVO® USPI; Larkin-2019). When combined with a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor, PD-1 blocking antibody had an ORR of 50%, median PFS of 11.5 months, and long-term survival rate of 52% (OPDIVO® USPI; Larkin-2019). Despite the improved outcomes with PD-1 blocking antibodies, more than 55% of patients do not respond to single-agent nivolumab or pembrolizumab and half do not respond to combination therapy with a CTLA-4 inhibitor. Therefore, there remains a critical need for innovative anticancer therapy in this condition.

There are several preferred Category 1 regimens (based upon high-level evidence and National Comprehensive Cancer Network consensus) available for the first-line treatment of patients with unresectable Stage III/IV melanoma, including PD-1 blockade monotherapy or, if a BRAF V600-activating mutation is present, a combination of agents targeted at BRAF and mitogen-activated protein kinase (MEK) (NCCN-2020). In certain circumstances, nivolumab combined with ipilimumab may be another option.

## 1.2. CMP-001

CMP-001 is a toll-like receptor 9 (TLR9) agonist composed of [redacted], a cytosine linked to a guanine by a phosphate bond (CpG) oligodeoxynucleotide (ODN). The VLP is composed of a capsid protein derived from bacteriophage Qbeta. G10 is an ODN that contains CpG and poly-G tails that allow it to form G-quadruplexes. Once administered to a patient, an antidrug antibody response to the VLP (anti-Qbeta antibodies) develops. Antibody-coated [redacted] is taken up by cells through Fc receptors into the endosome. In plasmacytoid dendritic cells (pDCs), antibody-coated [redacted] is taken up via FcγRIIA into endosomes where the G10 is released and activates TLR9 (Lemke-Miltner-2020).

Toll-like receptor 9 is found in pDCs and B cells, but Type A CpG compounds have little effect on B cells. Plasmacytoid dendritic cells primarily reside in blood but can also be found in tumors and lymph nodes. Inactivated tumor-infiltrating pDCs contribute to tumor growth and are associated with an adverse prognosis in patients with cancer (Lombardi-2015; Demoulin-2013). Activation and maturation of pDCs through TLR9 agonism induces Type I interferons (IFNs), which in turn mediate the release of IFN-inducible chemokines such as C-X-C motif chemokine 9 and C-X-C motif chemokine 10 (CXCL10) (Swiecki-2015). Activated pDCs also take up tumor specific antigens for presentation to T cells and other immune cells, facilitating the development of an antigen-specific, antitumor T-cell response.

Together, the Type I IFNs, IFN-inducible chemokines, and antigen presentation promote the activation and differentiation of cluster of differentiation (CD) $8^+$ T cells into cytotoxic T lymphocytes (CTLs) capable of circulating throughout the body and attacking distant tumor cells. Therefore, administration of intratumoral (IT) CMP-001 is hypothesized to change the pDC functional phenotype from tumor promoting to one that promotes an antigen-specific, antitumor $CD8^+$ T cell response.

### 1.2.1. Previous Clinical Studies With CMP-001

The safety and efficacy data demonstrating the clinical benefit of CMP-001 IT in combination with pembrolizumab intravenous (IV) in patients with melanoma refractory to PD-1 blockade were obtained in an ongoing clinical study, Study CMP-001-001 (Milhem -2020). In the 98 subjects treated with pembrolizumab according to the KEYTRUDA® (pembrolizumab) United States Prescribing Information (KEYTRUDA® USPI) in combination with CMP-001 10 mg IT every week for 7 weeks and every 3 weeks (Q3W) thereafter, the objective response rate (ORR) was 27.6% (27/98; 95% confidence interval [CI] 19.0%, 37.6%), including patients with responses after initial progressive disease and the best ORR by RECIST v1.1 was 23.5% (23/98; 95% CI: 15.5%, 33.1%), including 7 complete responses and 16 partial responses. This ORR is substantially higher than the 7.7% response rate observed in the 6 of 78 patients who received treatment beyond progression with pembrolizumab in the Keynote-002 study (Ahmed-2020). The clinical benefit of this combination treatment includes durable CRs and PRs in injected and non-injected target lesions and non-target lesions of the skin, lymph nodes, and viscera. The Kaplan-Meier estimate for median duration of response (DOR) for both RECIST v1.1 responders and RECIST v1.1 responders plus post-progressive disease responders was 19.9 months (95% CI: 6 months, 19.9 months). Most treatment related adverse events (TRAEs) were Grade 1 or 2 and included flu-like symptoms, including chills, fever, fatigue, nausea, vomiting, and headache, and injection site pain. The most common treatment-related Grade 3 or 4 adverse events were hypotension (6.3%) and hypertension (5.0%). No Grade 5 treatment-related adverse events were reported. Additional information is provided in the CMP-001 Investigator's Brochure (IB).

Preliminary safety and efficacy data from an ongoing Phase 2 Investigator Sponsored Trial of CMP-001 IT in combination with nivolumab in subjects with high-risk resectable melanoma (Study HCC 17-169) demonstrated clinical activity and a tolerable safety profile (Davar -2020). Pathological responses, defined as ≤ 50% residual viable tumor (RVT), were reported in 70% of subjects 21/30) and included pathological complete response (pCR), defined as 0% RVT, in 50% (15/30) of subjects, pathological major response (pMR), defined as 1% to 10% RVT, in 10% (3/30) of subjects, and pathological partial response (pPR), defined as 11% to 50% RVT, in 10% (3/30) of subjects. In the 31 subjects evaluable for safety, CMP-001 in combination with nivolumab was generally well tolerated with an acute toxicity profile consisting predominantly of Grade 1 or 2 TRAEs. The only treatment-related Grade 3 adverse event in more than 1 subject was hypertension (n = 3, 9.7%). No Grade 4/5 TRAEs were reported. There were no dose limiting toxicities or delays in surgery related to neoadjuvant treatment. One-year regression free survival was 89% in patients with major pathological response (pCR and pMR) and 90% in patients with any pathological response (pCR, pMR, and pPR).

## 1.3. Nivolumab

### 1.3.1. Nivolumab Mechanism of Action

Nivolumab (also referred to as BMS-936558, MDX1106, or ONO-4538) is a human monoclonal antibody (HuMAb; immunoglobulin G4-S228P) that targets the PD-1 cluster of differentiation 279 cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes (Schadendorf 2017). Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration.

Nivolumab is approved for the treatment of several types of cancer in multiple regions including the US (Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014).

### 1.3.2. Nivolumab Clinical Activity

Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy in several tumor types, including non-small cell lung cancer (NSCLC), melanoma, renal cell carcinoma (RCC), classical Hodgkin lymphoma (cHL), small cell lung cancer, gastric cancer, squamous cell carcinoma of the head and neck (SCCHN), urothelial cancer, hepatocellular carcinoma (HCC), and colorectal cancer (CRC). In confirmatory trials, nivolumab as monotherapy demonstrated a statistically significant improvement in OS as compared with the current standard of care in patients with advanced or metastatic NSCLC, unresectable or metastatic melanoma, advanced RCC, or SCCHN. Details of the clinical activity in these various malignancies are provided in the nivolumab Investigator's Brochure.

### 1.3.3. Benefit/Risk Assessment

Extensive details on the safety profile of nivolumab are available in the nivolumab Investigator's Brochure and will not be repeated herein.

Overall, the safety profile of nivolumab monotherapy is manageable and generally consistent across completed and ongoing clinical trials with no maximum tolerated dose reached at any dose tested up to 10 mg/kg. Most AEs were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level.

A pattern of immune-related AEs has been defined, for which management algorithms have been developed; these are provided in Appendix H. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.

Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the nivolumab Investigator's Brochure.

## 1.4. Study Rationale

### 1.4.1. Rationale for Combining a TLR9 Agonist with an PD-1 Blocking Antibody

PD-1 blockade is an effective and important therapy for the treatment of melanoma, however, more than 60% of patients do not respond to monotherapy treatment with a PD-1 blocking antibody. PD-1 negatively regulates T cell function when it interacts with its ligand PD-L1, which is commonly expressed on tumors (Chen-2013). A major mechanism of resistance to PD-1 blockade is the absence of activated effector T cells in the tumor. Therefore, TLR9-mediated T cell activation and trafficking to tumor has the potential to improve the response to PD-1 blockade, particularly in non-inflamed tumors.

In prior clinical trials, TLR9 agonism resulted in strong induction of CTL responses; however, very few objective responses were observed and the T cell responses were not sustained, especially within tumors (Appay-2006). This may be because TLR9-mediated T cell activation induces PD-1 expression on activated T cells (Fourcade-2014). TLR9 agonists are capable of inducing tumor-specific $CD8^+$ T cells in cancer subjects, but the expression of PD-1 on these T cells blocks their function. Therefore, PD-1 blockade may facilitate and sustain the TLR9-mediated activation of tumor-specific T cells.

Several nonclinical and clinical reports support the hypothesis that TLR9 agonism may enhance the antitumor response of melanoma to PD-1 blockade. The ex vivo addition of a PD-1–blocking antibody to $CD8^+$ T cells from melanoma subjects who had been treated with a TLR9 agonist significantly increased the T cell function for cytokine secretion (Fourcade-2014), providing a rationale for the use of the combination of TLR9 agonists and PD-1–blocking antibodies in cancer therapy.

Several TLR9 agonists have shown antitumor efficacy in mouse tumor models in combination with PD-1 blockade. In mice with MB49 bladder cancer, a CpG-B ODN in combination with anti-CTLA-4 or anti-PD-1 increased survival, and PD-1 blockade plus CpG treatment was superior to either agent alone. CpG plus anti-CTLA-4 or anti-PD-1 increased the numbers of circulating tumor-specific, CD107a-expressing $CD8^+$ T cells as well as activated ($CD25^+FoxP3^-$) CD4 splenocytes. Furthermore, regulatory T cells were decreased in the tumor area of treated animals after anti-CTLA-4 or anti-PD-1 plus CpG therapy (Mangsbo-2010). Additionally, mice treated with a CpG-B TLR9 agonist in combination with PD-1 blockade in an ovarian cancer model also had improved survival (Duraiswamy-2013). Mechanistic studies in the PD-L1 resistant mouse tumor models, including CT26 and MC38 colon carcinoma and TSA mammary adenocarcinoma, demonstrated that IT injection of a CpG-C ODN reversed resistance to PD-1 blockade by inducing the infiltration of activated $CD8^+$ T cells expressing IFN gamma (Wang-2016). Finally, injection of CMP-001 IT in a mouse A20 lymphoma model reduced the growth of both injected and noninjected tumors and improved survival, and these antitumor effects were enhanced by combination with systemic anti-PD-1 therapy (Lemke-Miltner-2020). The VLP appeared to contribute to the antitumor efficacy of CpG-A therapy, since a reduced antitumor effect was observed if the CpG-A TLR9 agonist was administered without the VLP.

### 1.4.2. Rationale for Intratumoral Administration of TLR9 Agonists

CMP-001 is intended to activate pDCs via TLR9 agonism, which causes the pDCs to release Type I IFN and take up and present tumor antigens to T cells, culminating in the generation of an antigen-specific, antitumor T cell response. Administration of CMP-001 IT is intended to activate pDCs, and subsequently T cells, within the tumor and tumor-draining lymph nodes

where tumor-specific antigen is most likely to exist. Systemic administration of TLR9 agonists is expected to result in uptake by the liver, spleen, and reticuloendothelial system, which may lead to suboptimal activation of pDCs in tumor and tumor-draining lymph nodes.

Intratumoral administration of CMP-001 is expected to activate resting pDCs, thereby overcoming their tumor-promoting phenotype and ultimately inducing an antitumor $CD8^+$ T cell response in the tumor microenvironment. In preclinical models, IT dosing of TLR9 agonists was more effective than distant subcutaneous (SC) dosing, and induced regression not only in the directly injected tumor lesion, but also distant metastases (Heckelsmiller-2002; Shirota-2012).

### 1.4.3. Rationale for CMP-001 Dose and Schedule

In the dose escalation phase of Study CMP-001-001, CMP-001 IT was evaluated at doses of 1 to 10 mg IT using 2 different dosing schedules and with preparations containing 2 different concentrations of the excipient polysorbate 20 (PS20) (0.01% and 0.00167%) in combination with pembrolizumab IV in subjects with PD-1 refractory melanoma. The safety profile was similar and manageable at all CMP-001 doses of 1 to 10 mg. Antitumor activity, including durable complete and partial responses, with a predictable/manageable safety profile was observed in 23% of subjects who initiated treatment with the proposed dose and schedule for this study: CMP-001 10 mg (PS20 0.01%) IT QW for 7 doses, followed by administration Q3W in combination with pembrolizumab 200 mg IV Q3W. This dose and schedule were selected for further development.

Further details can be found in the CMP-001 Investigator's Brochure.

### 1.4.4. Rationale for Nivolumab Dose and Schedule

The rationale for administering nivolumab Q3W is to align with the schedule of CMP-001 evaluated in Study CMP-001-001. Population PK analyses have shown that the PK of nivolumab is linear, with proportional exposures over a dose range of 0.1 to 10 mg/kg. The benefit-risk profiles of nivolumab 240 mg every 2 weeks (Q2W), 360 mg Q3W, and 480 mg every 4 weeks (Q4W) are predicted to be comparable to 3 mg/kg Q2W. This is further discussed in Section 5.1.1.1.

### 1.4.5. Rationale for Open Label Randomized, Controlled Trial

A randomized, controlled trial comparing CMP-001 in combination with nivolumab versus nivolumab monotherapy was designed to address the contribution of CMP-001 to the combination of CMP-001 with PD-1 blockade. Confirmed ORR assessed by Blinded Independent Central Review (BICR) using RECIST v1.1 is the Phase 2 primary endpoint to provide an early assessment of benefit and risk, without compromising the Phase 3 primary endpoint of PFS, prior to enrolling the larger Phase 3 population. The rationale for an open-label study is based on the fact that a blinded study would require subjects assigned to placebo to unnecessarily receive the pretreatment prophylaxis, have a sham procedure performed, and potentially prolong the time in the clinic to receive the additional study treatment. These risks were perceived to outweigh the benefits to the rigor of the study and the lack of placebo control is not expected to impact the veracity of the results.

# 2. STUDY OBJECTIVES AND ENDPOINTS

## 2.1. Phase 2 Study Objectives

### 2.1.1. Phase 2 Primary Objective

The primary objective of the Phase 2 portion of the study is to determine confirmed ORR for treatment with first-line CMP-001 in combination with nivolumab versus nivolumab monotherapy in subjects with unresectable or metastatic melanoma.

### 2.1.2. Phase 2 Secondary Objective

The secondary objective of the Phase 2 portion of the study is to evaluate the safety and tolerability of first-line CMP-001 in combination with nivolumab versus nivolumab monotherapy in subjects with unresectable or metastatic melanoma.

## 2.2. Phase 3 Study Objectives

### 2.2.1. Phase 3 Primary Objective

The primary objective of the Phase 3 portion of the study is to evaluate PFS for subjects receiving first-line CMP-001 in combination with nivolumab versus nivolumab monotherapy for unresectable or metastatic melanoma.

### 2.2.2. Phase 3 Secondary Objectives

The secondary objectives of the Phase 3 portion of the study are to:

- Evaluate the safety and tolerability of first-line CMP-001 in combination with nivolumab versus nivolumab monotherapy in subjects with unresectable or metastatic melanoma
- Evaluate the efficacy of first-line CMP-001 in combination with nivolumab versus nivolumab monotherapy in subjects with unresectable or metastatic melanoma

### 2.2.3. Phase 3 Exploratory Objectives

The exploratory objectives of the Phase 3 portion of the study are to:

- [redacted]
- [redacted]

## 2.3. Phase 2 Study Endpoints

### 2.3.1. Phase 2 Primary Endpoint

The primary endpoint in the Phase 2 portion of the study is the ORR defined as the proportion of subjects with a confirmed objective response of CR or PR based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) as determined by BICR.

### 2.3.2. Phase 2 Secondary Endpoints

The secondary endpoint in the Phase 2 portion of the study is AEs, SAEs, and AEs leading to discontinuation or death and severity of AEs as assessed by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

## 2.4. Phase 3 Study Endpoints

### 2.4.1. Phase 3 Primary Endpoint

The primary endpoint in the Phase 3 portion of the study is PFS defined as the time from the date of randomization to first date of documented progressive disease based on RECIST v1.1 by BICR or death from any cause, whichever occurs first.

### 2.4.2. Phase 3 Secondary Endpoints

The secondary endpoints in the Phase 3 portion of the study are:

- AEs, SAEs, and AEs leading to discontinuation or death and severity of AEs as assessed by NCI CTCAE v5.0
- OS, defined as the time from the date of randomization until death from any cause.
- Confirmed ORR, defined as the proportion of subjects with a confirmed objective response of CR or PR based on RECIST v1.1 as determined by BICR
- DOR, defined as the time from date of first documented response (CR or PR) to date of documented progressive disease, based on RECIST v1.1 as determined by BICR
- Disease control rate (DCR), defined as the proportion of subjects who have a confirmed best response of CR or PR, or stable disease (SD) lasting at least 4 months, based on RECIST v1.1 as determined by BICR
- Treatment response in noninjected target lesions based on RECIST v1.1 by Investigator
- PFS, ORR, DOR, and DCR based on RECIST v1.1 and immune PFS (iPFS), immune DOR (iDOR), and immune ORR (iORR) based on immunotherapy RECIST (iRECIST) as determined by Investigator assessment

### 2.4.3. Phase 3 Exploratory Endpoints

The exploratory endpoints in the Phase 3 portion of the study are:

- [redacted]
- Change from Baseline in blood concentrations of CXCL10 after treatment with CMP-001
- Baseline, and change from Baseline, in tumor or blood measurements of biomarkers related to TLR9 (data from Phase 2 portion of the study)

# 3. INVESTIGATIONAL PLAN

## 3.1. Overall Study Design

This is a randomized, open-label, active-control study of first-line CMP-001 administered by intratumoral (IT) injection in combination with intravenous (IV) nivolumab versus nivolumab monotherapy in subjects with Stage III or IV unresectable or metastatic melanoma who have not been previously treated with a programmed cell death protein 1 (PD-1) blocking antibody for metastatic disease. Subjects will be randomized in a 1:1 manner to Arm A to receive CMP-001 IT in combination with nivolumab IV or Arm B to receive nivolumab monotherapy according to the Schedule of Assessments (Table 1) and Section 5.1.

The study will follow a Phase 2/3 design. Eligible subjects will be enrolled in the Phase 2 portion of the study; enrollment into the Phase 3 portion of the study will not proceed until the primary endpoint of Phase 2 is evaluated.

The Phase 2 primary endpoint of ORR per RECIST v1.1 as determined by BICR will be assessed approximately 30 weeks after the last subject is randomized into the Phase 2 portion of the study. If the primary endpoint of Phase 2 is met, subjects enrolled in the Phase 2 portion of the study will continue to receive study treatment (in Arm A or Arm B) in the Phase 3 portion of the study, and enrollment will proceed in Phase 3. If the Phase 2 primary endpoint is not met, subjects enrolled in Phase 2 may remain in the study and continue to receive study treatment until a reason for treatment discontinuation is reached but no further subjects will be enrolled. An Independent Data Monitoring Committee (IDMC) will review safety and efficacy data throughout the study.

Disease assessments by computed tomography (CT) or magnetic resonance imaging (MRI) and other appropriate measures will be performed beginning predose at Week 10 Day 1 (W10D1) (-7 days) and will be repeated every 6 weeks (eg, W16D1). Responses (CR, PR, iCR, or immune PR [iPR]) will be confirmed by a follow-up disease assessment performed at least 4 weeks after the initial response date. Disease assessments will continue every 6 weeks while the subject is on treatment. Disease assessments will be conducted every 12 weeks for subjects on study after 1 year. All scans should be performed at least 2 weeks after the previous CMP-001 IT injection to prevent injection-related pseudoprogression. Imaging should not be delayed for delays in treatment.

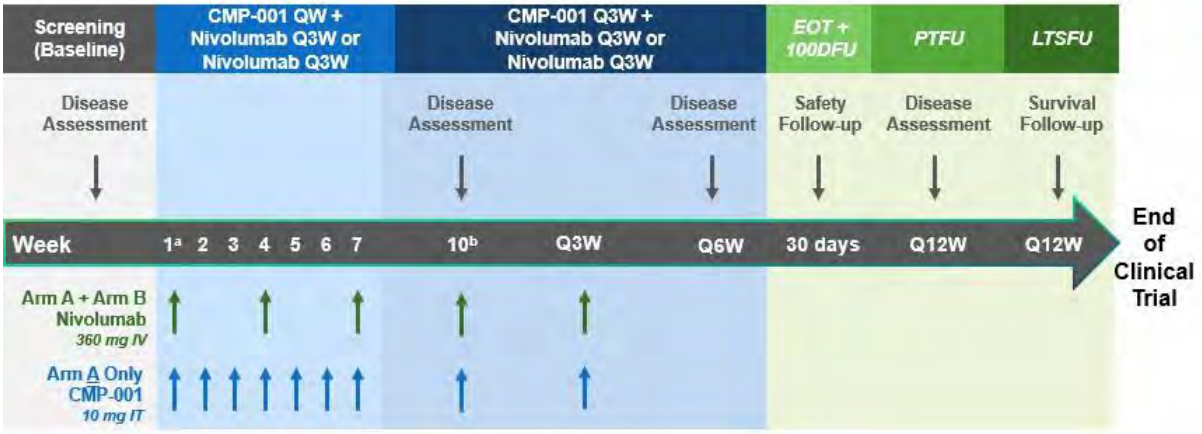
Subjects may continue to receive study treatment beyond progressive disease (PD) according to RECIST v1.1 and will be evaluated by the Investigator according to iRECIST. Subjects with PD per RECIST v1.1 as determined by Investigator assessment should remain on treatment per Investigator discretion and have a follow-up scan performed at least 4 weeks after the initial date of PD to confirm progression per RECIST v1.1.

Subjects who discontinue study treatment should complete an end of treatment (EOT) visit and 100-day safety follow-up contact, which should occur 100 days (+7) after EOT or until an alternative cancer treatment is initiated, whichever occurs first. Subjects who are post-treatment but have not met criteria for study discontinuation should remain on study for post-treatment follow-up (PTFU) and long-term survival follow-up (LTSFU) and receive study evaluations for efficacy according to the Schedule of Assessments (Table 1).

At the end of the treatment period (2 years), the Sponsor will not continue to provide supplied study treatment to subjects/investigators unless the Sponsor chooses to extend the study. The Investigator should ensure that the subjects receive appropriate standard of care to treat the condition under study.

The study design for is summarized in Figure 1.

**Figure 1: CMP-001-011 Study Schema**




Abbreviations: 100DFU = 100-Day Follow-up; EOT = End of Treatment; LTSFU = Long-Term Survival Follow-up; IT = intratumoral; IV = intravenous; PTFU = Post-treatment Follow-up; Q3W = every 3 weeks; Q6W = every 6 weeks; Q12W = every 12 weeks; QW = weekly; W1D1 = Week 1 Day 1; W10D1 = Week 10 Day 1.

a The first CMP-001 dose (W1D1) may be administered subcutaneously or by IT injection at the discretion of the Investigator.

[redacted]

## 3.2. Duration of Treatment with Nivolumab

The optimal duration of immunotherapy is an important question and continues to be investigated. Clinical trials across different tumors types in the nivolumab and ipilimumab development program indicate that most of the responses occur early, with a median time to response of 2 to 4 months, and emerging data suggest that benefit can be maintained in the absence of continued treatment. A retrospective pooled analysis of 2 melanoma studies suggest the majority of patients who discontinue nivolumab and/or ipilimumab for toxicity maintain disease control in the absence of further treatment (Schadendorf-2017). Furthermore, a limited duration of ipilimumab, including only 4 induction doses, resulted in long-term survival in patients with metastatic melanoma, with a sustained plateau in survival starting around 2 years after the start of treatment (Schadendorf-2015).

Accumulating data suggest that 2 years of treatment with a PD-1 checkpoint inhibitor may be sufficient for long-term benefit. CA209003, a dose-escalation cohort expansion trial evaluating the safety and clinical activity of nivolumab in patients with previously treated advanced solid tumors (including 129 subjects with NSCLC), specified a maximum treatment duration of 2 years. Among 16 subjects with NSCLC who discontinued nivolumab after completing 2 years of treatment, 12 subjects were alive >5 years and remained progression-free without any subsequent therapy. In the CA209003 NSCLC cohort, the OS curve begins to plateau after 2 years, with an OS rate of 25% at 2 years and 18% at 3 years (Brahmer-2017). These survival outcomes are similar to Phase 3 studies in previously treated NSCLC, in which nivolumab treatment was continued until progression or unacceptable toxicity (2-year OS rates of 23% and 29%, and 3-year OS rates of 16% and 18% for squamous and non-squamous NSCLC, respectively) (Felip-2017).

Taken together, these data suggest that treatment beyond 2 years is unlikely to confer additional clinically meaningful benefit and that the risk of progression after discontinuing treatment at 2 years is low.

In contrast, a shorter duration of nivolumab of only 1 year was associated with increased risk of progression in previously treated patients with NSCLC, suggesting that treatment beyond 1 year is likely needed. In CA209153, patients with previously treated advanced NSCLC who completed 1 year of nivolumab therapy were randomized to either continue or stop treatment, with the option of retreatment upon progression. Among 163 patients still on treatment at 1 year and without progression, those who were randomized to continue nivolumab had significant improvement in (PFS compared to those who were randomized to stop treatment, with median PFS (post-randomization) not reached vs 10.3 months, respectively; hazard ratio (HR) = 0.42 (95% CI: 0.25, 0.71). With a median follow-up of 14.9 months post-randomization, there also was a trend for patients on continued treatment to live longer (OS HR = 0.63 [95% CI: 0.33, 1.20]). Of note, the PFS curves in both groups plateau approximately 1 year after randomization (ie, 2 years after treatment initiation), suggesting that there may be minimal benefit in extending treatment beyond a total of 2 years (Spigel-2017).

Collectively, these data suggest that there is minimal if any benefit derived from continuing immune-oncology treatment beyond 2 years in advanced tumors. Even though immunotherapy is well tolerated, subjects will be at risk for additional toxicity with longer term treatment. Therefore, in this study, treatment will be given for a maximum of 2 years from the start of study treatment.

## 3.3. Blinded Independent Central Review Committee

On-treatment disease assessments (MRI, CT scans, and photographic images) will be assessed by a BICR committee using RECIST v1.1 (see Section 7.2.). Further details are provided in the BICR charter.

## 3.4. Independent Data Monitoring Committee

An external IDMC will review interim safety and efficacy data during the study. The IDMC will make recommendations to the Sponsor throughout the study to ensure subject safety.

Members of the IDMC must not be involved with the study in any other way and must have no competing interest that could affect their roles with respect to the study.

The IDMC will have a finalized charter before their first meeting. Details regarding the roles and responsibilities of IDMC members, meeting facilitation, and proper documentation of IDMC reports will be provided in the charter.

# 4. SELECTION AND WITHDRAWAL OF SUBJECTS

## 4.1. Inclusion Criteria

Subjects enrolled in the study must meet all of the following inclusion criteria to be eligible.

1. Histologically or cytologically confirmed unresectable Stage III or Stage IV melanoma per American Joint Committee on Cancer (AJCC) Cancer Staging Manual Eighth Edition.
2. Measurable disease, as defined by RECIST v1.1 and all of the following:
   a. At least 1 accessible lesion amenable to repeated IT injection
   b. One or more measurable lesions at least 1 cm in diameter that are not intended for CMP-001 injection and can be followed as target lesions per RECIST v1.1
3. Able to provide tissue from a core or excisional/incisional biopsy (fine needle aspirate is not sufficient). A newly obtained biopsy (within 90 days before the first dose of study treatment) is mandatory, but an archival sample is acceptable if no intervening therapy for melanoma/cancer was received.

   Note: For tissue sampling details, please refer to the Laboratory Manual.
4. Adequate organ function based on most recent laboratory values within 3 weeks before the first dose of study treatment on W1D1:
   a. Bone marrow function:
      – neutrophil count $\geq 1500/mm^3$
      – platelet count $\geq 100\ 000/mm^3$
      – hemoglobin concentration ≥9 g/dL
      – white blood cell $\geq 2000/mm^3$
   b. Liver function:
      – total bilirubin ≤ 1.5 × the upper limit of normal (ULN) with the following exception: subjects with Gilbert Disease total serum bilirubin ≤3 × ULN
      – aspartate aminotransferase (AST) and alanine aminotransferase ≤3 × ULN
   c. Lactate dehydrogenase ≤2 × ULN
   d. Renal function: estimated (Cockcroft-Gault) or measured creatinine clearance ≥30 mL/min
   e. Coagulation
      – International normalized ratio (INR) or prothrombin time (PT) ≤1.5 × ULN, unless subject is receiving anticoagulant therapy, as long as PT or partial thromboplastin time (PTT) is within therapeutic range of intended use of anticoagulants
      – Activated partial thromboplastin time or ≤1.5 × ULN, unless subject is receiving anticoagulant therapy, as long as PT or PTT is within therapeutic range of intended use of anticoagulants

5. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1 at Screening.
6. Age ≥18 years at time of consent.
7. Capable of understanding and complying with protocol requirements.
8. Women of childbearing potential must have negative serum pregnancy test prior to dosing at W1D1 and be willing to use an adequate method of contraception (Section 4.3.2) from the time of consent until at least 150 days after the last dose of study treatment.
9. Able and willing to provide written informed consent and to follow study instructions. Subjects unable to provide written informed consent on their own behalf will not be eligible for the study.

## 4.2. Exclusion Criteria

Subjects presenting with any of the following will not qualify for entry into the study:

1. Uveal, acral, or mucosal melanoma.
2. Received prior systemic treatment for melanoma in the unresectable or metastatic setting. Prior adjuvant therapy is acceptable if the treatment course (of approximately 1 year duration) was completed and there was no recurrence within 6 months of the last dose of adjuvant treatment.
3. Received prior therapy with CMP-001.
4. Requires systemic pharmacologic doses of corticosteroids greater than the equivalent of 10 mg/day prednisone within 30 days before the first dose of study treatment on W1D1.
    a. Subjects who are currently receiving steroids at a prednisone-equivalent dose of ≤10 mg/day do not need to discontinue steroids prior to enrollment.
    b. Replacement doses, topical, ophthalmologic, and inhalational steroids are permitted.
5. History of CTCAE v5.0 Grade 4 immune-related AE due to adjuvant CTLA-4 or PD-1 blocking antibody.
6. Not fully recovered from AEs (to Grade 1 or less [per CTCAE v5.0], with the exception of persistent alopecia, adrenal insufficiency, and hypothyroidism) due to prior treatment.
7. Active pneumonitis, history of pneumonitis that required steroids, or history of interstitial lung disease.
8. Severe uncontrolled cardiac disease within 6 months of Screening, including but not limited to poorly controlled hypertension, unstable angina, myocardial infarction, congestive heart failure (New York Heart Association Class II or greater), pericarditis within the previous 6 months, cerebrovascular accident, and implanted or continuous use of a pacemaker or defibrillator.
9. Known history of immunodeficiency.
10. Known additional malignancy that has progressed or required active treatment within the past 3 years. Exceptions include basal cell carcinoma of the skin, squamous cell

carcinoma of the skin that has undergone potentially curative therapy, curatively treated localized prostate cancer with prostate-specific antigen level below 4.0 ng/mL, in situ cervical cancer on biopsy or a squamous intraepithelial lesion on Papanicolaou smear, thyroid cancer (except anaplastic), and adjuvant hormonal therapy for breast cancer > 3 years from curative-intent surgical resection.

11. Active autoimmune disease that has required systemic treatment in past 2 years; replacement therapy is not considered a form of systemic treatment.
12. Untreated, symptomatic, or enlarging central nervous system (CNS) metastases or carcinomatous meningitis (including leptomeningeal metastases from solid tumors).
13. Prior allogenic tissue/solid organ transplant.
14. Known or suspected active infection with severe acute respiratory syndrome coronavirus 2 virus (SARS-CoV-2).
15. Active infection requiring systemic therapy.
16. Known or suspected infection with HIV, hepatitis B virus, or hepatitis C virus; testing is not required unless suspected.
17. Received a live/attenuated virus vaccination within 30 days prior to the first dose of study treatment on W1D1.
18. Received blood products (including platelets or red blood cells) or colony stimulating factors (including granulocyte colony stimulating factor, granulocyte/macrophage colony stimulating factor, or recombinant erythropoietin) within 30 days prior to the start of Screening.
19. History of permanent discontinuation of nivolumab due to infusion reactions.
20. Any concurrent uncontrolled illness, including mental illness or substance abuse, which in the opinion of the Investigator, would make the subject unable to cooperate or participate in the trial.
21. Participation in another clinical study of an investigational anticancer therapy or device within 30 days before the first dose of study treatment on W1D1.

    Note: Participation in the follow-up phase (receiving no study treatment) of a prior study is allowed.
22. Requires prohibited treatment (ie, non-protocol specified anticancer pharmacotherapy, surgery, or conventional radiotherapy) for treatment of malignant tumor.
23. Has a life expectancy of less than 3 months and/or has rapidly progressing disease (eg, tumor bleeding, uncontrolled tumor pain) in the opinion of the treating Investigator.
24. Pregnant or breast-feeding or expecting to conceive or donate eggs within the projected duration of the study, from the time of consent until at least 150 days after the last dose of study treatment for women.

## 4.3. Women of Childbearing Potential

A woman of childbearing potential is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (Section 4.3.1). If fertility is unclear and a menstrual cycle cannot be confirmed before the first dose of study treatment (W1D1),

subject should be considered of childbearing potential and applicable pregnancy tests completed.

### 4.3.1. Women of Non-Childbearing Potential

Female subjects must meet 1 of the following criteria to be considered of non-childbearing potential:

- Have undergone hysterectomy or bilateral salpingectomy/oophorectomy or bilateral tubal occlusion/ligation at least 1 month before Informed Consent.
- Are medically confirmed to be post-menopausal. A postmenopausal state is defined as 12 months of amenorrhea before W1D1 in a woman over age 45 years in the absence of other biological or physiological causes.
  In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL on 2 measurements done 2 months apart to confirm menopause.

### 4.3.2. Acceptable Methods of Contraception

Heterosexually active female subjects of childbearing potential must agree to use a highly effective method of contraception for the duration of the study and at least 150 days after the last dose of study treatment. Women should not donate eggs during this period.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of <1% per year when used consistently and correctly (ie, perfect use) and include:

- Established use of oral, injected, or implanted hormonal methods of contraception
- Correctly placed intrauterine device or intrauterine system
- Sexual abstinence
- Vasectomized partner

## 4.4. Prohibited Concomitant Medications

The following medications are prohibited during the study (unless utilized to treat a drug-related AE):

- Immunosuppressive agents.
- Any concurrent systemic anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents for treatment of unresectable or metastatic melanoma).
- Any non-palliative radiation therapy.
- Any complementary medications (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study.
- Any live/attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio, and measles, mumps, rubella [MMR]) during treatment and until 100 days post last dose.
- Concurrent anticancer therapy with agents other than the combination drug therapy (CMP-001 or nivolumab) is not allowed at any time during the study.

- Chloroquine, hydroxychloroquine, and quinacrine, as these agents are known to have significant TLR9 antagonism.
- Systemic pharmacologic doses of corticosteroids greater than the equivalent of 10 mg/day prednisone are not permitted at the time of study enrollment with the following exceptions:
  - Allowed for subjects with a history of adrenal insufficiency. Consultation with the Medical Monitor is required prior to enrollment of subjects with a history of adrenal insufficiency;
  - Allowed for the management of immune-mediated toxicities;
  - Allowed for palliation of pain, brain metastases, or other disorders if subjects remain on study based on Investigator's judgement after consultation with Medical Monitor.
- Medications intended solely for supportive care (ie, antiemetics, analgesics, megestrol acetate for anorexia) are allowed.

Palliative radiotherapy or palliative surgery (ie, for pain, bleeding, spinal cord compression, brain metastasis, new or impending pathologic fracture, superior vena-cava syndrome, or obstruction) may be allowed after Medical Monitor consultation to ascertain whether clinical progression has occurred. If the lesion(s) targeted for palliation are target lesions, then the anatomic site requiring palliation must be assessed for disease status.

Given the potential for injection site reactions and flu-like symptoms, vaccination with a viral vector or mRNA vaccine should not be performed within 48 hours of CMP-001 injection.

## 4.5. Treatment Discontinuation

Treatment discontinuation is defined as any subject who stops receiving study treatment and does not restart within 12 weeks. Subjects who permanently discontinue (for >12 weeks) CMP-001 or nivolumab may not be re-treated with the discontinued study treatment in this study. When nivolumab is permanently discontinued due to an immune related AE, CMP-001 must also be permanently discontinued.

Treatment with study treatment should continue until one of the following occurs:

- Unacceptable AE that precludes further study treatment
- 2 years of study treatment
- PD per RECIST v1.1; continuation of treatment through suspected pseudoprogression is permitted at the Investigator's discretion until confirmed PD per iRECIST
- Upon request of the Sponsor or regulatory agency
- Clinical disease progression in the opinion of the Investigator
- If medically necessary in the opinion of the Investigator
- Subject withdraws consent for study treatment
- Subject has received study treatment for 2 years
- Subject becomes pregnant or begins breastfeeding

- Subject is lost to follow-up
- Death
- End of Clinical Trial

If a subject achieves and maintains a confirmed CR or iCR by Investigator assessment, IT or SC injections of CMP-001 or the combination of CMP-001 and nivolumab may be discontinued at the Investigator's discretion once the subject meets both of the following criteria:

- Subject has been treated for at least 48 weeks (the maximum duration of study treatment is 2 years)
- Subject has received at least 3 doses of assigned treatment beyond the date of the initial CR/iCR

Subjects with PD per RECIST v1.1 as determined by Investigator assessment should remain on treatment and have a follow-up scan performed at least 4 weeks after the initial date of PD to confirm progression per RECIST v1.1 by BICR.

Subjects who discontinue study treatment should complete an EOT visit and 100-day safety follow-up contact, which should occur 100 days (+7) after the EOT or until an alternative cancer treatment is initiated, whichever occurs first (Table 1). Subjects who discontinue study treatment for reasons other than disease progression (either per RECIST v1.1 or iRECIST by Investigator assessment) should remain on study for PTFU (Section 7.6) and receive disease assessments according to the Schedule of Assessments (Table 1).

## 4.6. Study Discontinuation

Subjects may withdraw from the study at any time without penalty or loss of future medical care or any other benefits to which they are otherwise entitled. Subjects will be withdrawn from the study for any of the following reasons:

- Subject withdraws consent for the study
- Subject lost to follow-up
- Death
- End of Clinical Trial

Subjects who withdraw consent from overall study participation (not only study treatment) will not have the EOT visit, safety follow-up visits, or further evaluations performed.

## 4.7. End of Clinical Trial

The End of Clinical Trial is defined as the last visit for the last subject on the trial.

# 5. TREATMENT OF SUBJECTS

## 5.1. Administration of Study Treatment

### 5.1.1. Nivolumab

Subjects will receive CMP-001 10 mg IT injection followed by nivolumab 360 mg IV (Arm A) or nivolumab 360 IV monotherapy (Arm B) at W1D1 and Q3W thereafter until the subject satisfies a condition for study treatment discontinuation. Nivolumab should be administered to the subject according to the nivolumab Investigator's Brochure. Nivolumab should be administered until the subject satisfies a condition for study treatment discontinuation (Section 4.5.). On visits where both study treatments are administered, nivolumab should be administered after CMP-001. There is no specified waiting period between the end of CMP-001 administration and the initiation of nivolumab infusion.

Subjects should receive nivolumab at a dose of 360 mg as a 30-minute infusion each treatment cycle until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

There will be no dose escalations or reductions of nivolumab allowed. Subjects may be dosed no less than 19 days from the previous dose.

Subjects should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, subjects should be managed according to Section 5.1.4.

Doses of study treatment(s) may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment. Dosing visits are not skipped, only delayed.

The assessment for discontinuation of nivolumab should be made separately from the assessment made for discontinuation of CMP-001. If discontinuation criteria are met for CMP-001 but not for nivolumab, treatment with nivolumab may continue if CMP-001 is discontinued.

Please refer to the nivolumab Investigator's Brochure and/or Pharmacy Manual for further details regarding storage, preparation, and administration of nivolumab.

Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

#### 5.1.1.1. Nivolumab Dose Selection

The nivolumab dose of 360 mg Q3W was selected based on clinical data and modeling and simulation approaches using population pharmacokinetics (PPK) and exposure-response (ER) analyses of data from studies in multiple tumor types (melanoma, NSCLC, and RCC) where body weight normalized dosing (mg/kg) was used.

Nivolumab pharmacokinetics (PK) have been extensively studied in multiple tumor types, including melanoma, NSCLC, RCC, cHL, SCCHN, CRC, and urothelial carcinoma and has been safely administered at doses up to 10 mg/kg Q2W. Nivolumab monotherapy was originally approved as a body-weight based dose of 3 mg/kg Q2W and was updated to 240 mg Q2W or 480 mg Q4W in multiple indications nivolumab Investigator's Brochure. Nivolumab 360 mg Q3W is also under evaluation in monotherapy and in combination therapy studies. Less frequent 360 mg Q3W and 480 mg Q4W dosing regimens can reduce

the burden to subjects of frequent, lengthy IV treatments and allow combination of nivolumab with other agents using alternative dosing regimens.

The benefit-risk profiles of nivolumab 240 mg Q2W, 360 mg Q3W, and 480 mg Q4W are predicted to be comparable to 3 mg/kg Q2W. This assessment is based on a comprehensive characterization of nivolumab PK, safety, efficacy, and ER relationships across indications. Population PK (PPK) analyses have shown that the PK of nivolumab is linear with proportional exposures over a dose range of 0.1 to 10 mg/kg; no clinically meaningful differences in PK across ethnicities and tumor types were observed. Using the PPK model, the exposures following administration of several dosing regimens of nivolumab administered as a flat dose were simulated, including 240 mg Q2W, 360 mg Q3W, and 480 mg Q4W. The simulated average serum concentration at steady state following administration of nivolumab 360 mg Q3W and 480 mg Q4W are predicted to be similar to those following administration of nivolumab 240 mg Q2W and nivolumab 3 mg/kg Q2W administered to subjects over a wide body weight range (34-180 kg) across tumor types.

Nivolumab ER relationships for efficacy and safety were evaluated for IV nivolumab administered as monotherapy at the dose range of 1 mg/kg Q2W to 10 mg/kg Q2W. Generally a flat ER relationship was observed over this dose range in melanoma, RCC, and NSCLC subjects between nivolumab exposure and clinical endpoints such as the hazard of death, probability of overall response, AE leading to discontinuation or death, Grade 3 or higher AEs, and/or Grade 2 or higher immune-mediated AEs. Therefore, 3 mg/kg IV Q2W was approved in melanoma, RCC, and NSCLC and was also studied and approved in other indications. For NSCLC, there was a trend of additional benefit (especially in ORR) at 3 mg/kg IV Q2W when compared to 1 mg/kg IV Q2W, which had a small sample size. Therefore, a flat ER relationship could only be confirmed from 3 mg/kg IV Q2W to 10 mg/kg IV Q2W for NSCLC. Flat doses of 240 mg IV Q2W nivolumab, 360 mg IV Q3W nivolumab, and 480 mg IV Q4W nivolumab have been incorporated in monotherapy and combination oncology studies, and the 240 mg IV Q2W and 480 mg IV Q4W nivolumab dose regimens are now approved in multiple indications. Every 4 week (Q4W) dosing regimens can reduce the burden to subjects of frequent, lengthy IV treatments and allow combination of nivolumab with other agents using alternative dosing regimens.

Extensive ER analyses using multiple PK measures (maximum serum concentration in Cycle 1, average serum concentration at Day 28 [$C_{avg28}$], and trough serum concentration at Day 28 [$C_{min28}$]) and efficacy and safety endpoints indicated that the efficacy of the flat-dose 480 mg IV regimen is similar to that of 3 mg/kg IV Q2W. In ER efficacy analyses for OS and ORR conducted in melanoma, RCC, and NSCLC using $C_{avg28}$ as the driver of efficacy, probabilities of achieving a response and survival probabilities at 1 year and 2 years for 480 mg IV Q4W were similar to that of 3 mg/kg IV Q2W.

Similar analyses conducted in different tumor types using the $C_{min28}$ as the worst-case scenario for the potential loss of efficacy also showed benefit risk profiles of 480 mg IV Q4W were comparable to 3 mg/kg IV Q2W.

#### 5.1.1.2. Clinical Pharmacology Summary

Nivolumab PK was assessed using a PPK approach for both single-agent nivolumab and nivolumab with ipilimumab.

*Nivolumab as a single agent:* The PK of single-agent nivolumab was studied in patients over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of nivolumab as a 60-minute IV infusion Q2W or Q3W. Nivolumab clearance (CL) decreases

over time, with a mean maximal reduction (% coefficient of variation [CV%]) from Baseline values of 24.5% (47.6%) resulting in a geometric mean steady-state clearance ($CL_{ss}$) (CV%) of 8.2 mL/h (53.9%) in patients with metastatic tumors; the decrease in $CL_{ss}$ is not considered clinically relevant. Nivolumab clearance does not decrease over time in patients with completely resected melanoma, as the geometric mean population clearance is 24% lower in this patient population compared with patients with metastatic melanoma at steady state. The geometric mean volume of distribution at steady state (CV%) is 6.8 L (27.3%), and geometric mean elimination half-life (CV%) is 25 days (77.5%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was 3.7-fold. The exposure to nivolumab increased in a dose proportional manner over the dose range of 0.1 to 10 mg/kg administered Q2W. The predicted exposure (average serum concentration and maximum serum concentration) of nivolumab after a 30-minute infusion is comparable to that observed with a 60-minute infusion.

*Specific Populations:* The PPK analysis suggested that the following factors had no clinically important effect on the CL of nivolumab: age (29 to 87 years), weight (35 to 160 kg), gender, race, Baseline lactate dehydrogenase PD-L1 expression, solid tumor type, tumor size, renal impairment, and mild hepatic impairment.

*Renal Impairment:* The effect of renal impairment on the CL of nivolumab was evaluated by a PPK analysis in patients with mild (estimated glomerular filtration rate [eGFR] 60 to 89 mL/min/1.73 $m^2$), moderate (eGFR 30 to 59 mL/min/1.73 $m^2$), or severe (eGFR 15 to 29 mL/min/1.73 $m^2$) renal impairment. No clinically important differences in the clearance of nivolumab were found between patients with renal impairment and patients with normal renal function.

*Hepatic Impairment:* The effect of hepatic impairment on the CL of nivolumab was evaluated by population PK analyses in patients with HCC and in patients with other tumors with mild hepatic impairment (total bilirubin [TB] ≤ ULN and AST > ULN or TB > 1 to 1.5 × ULN and any AST) and in HCC patients with moderate hepatic impairment (TB > 1.5 to 3 × ULN and any AST). No clinically important differences in the clearance of nivolumab were found between patients with mild/moderate hepatic impairment.

Details on the clinical pharmacology aspects of nivolumab can be found in the nivolumab Investigator's Brochure.

### 5.1.2. CMP-001

Subjects randomized to Arm A will receive CMP-001 10 mg weekly for 7 doses (W1D1 to W7D1), after which CMP-001 will be administered by IT injection Q3W (W10D1, W13D1, etc.). The first dose of CMP-001 may be administered SC or by IT injection, at the discretion of the Investigator; all subsequent doses are planned to be administered IT. The initial 7 CMP-001 weekly dose schedule must be completed before starting the Q3W CMP-001 dosing schedule.

On visits where both CMP-001 and nivolumab are administered, CMP-001 should always be administered before nivolumab. There is no waiting period between the end of CMP-001 administration and the initiation of nivolumab infusion.

CMP-001 should be administered until a reason for treatment discontinuation is reached (Section 4.5).

See Section 5.1.3 for dose modifications for CMP-001.

#### 5.1.2.1. Prophylaxis Prior to CMP-001 Injection

To prevent or reduce the severity of symptoms associated with CMP-001 administration, prophylaxis is required. Institutional regimens for prophylaxis related to cytokine release may be followed but only after discussion with the Medical Monitor; otherwise, the recommended regimen should be completed prior to initiation of CMP-001 injections:

- Intravenous fluids (eg, approximately 500 to 1000 cc IV normal saline; the volume is at the Investigator's discretion)
- Antipyretics (eg, acetaminophen 1000 mg and a non-steroidal anti-inflammatory agent such as indomethacin 50 mg or ibuprofen 600 to 800 mg)
- Antiemetics (eg, oral ondansetron 8 mg)
- Antihistamine (eg, oral diphenhydramine 50 mg, with or without an H2-antagonist)
- Recommended: hydrocortisone 25 mg at the Investigator's discretion. Subjects with adrenal insufficiency should be treated with stress dose steroids as described in Section 5.1.2.1.1.

Maintenance IV fluids should be continued after the CMP-001 injection during the observation period for continued fluid administration to minimize the risk for hypotension. Antipyretics and antiemetics may be repeated at the Investigator's discretion. There is no waiting period between the end of prophylaxis and the start of the CMP-001 injection. All treatments given prophylactically before and after CMP-001 dosing must be recorded for each visit.

##### 5.1.2.1.1. Prophylaxis for Subjects with a History of Adrenal Insufficiency

Subjects with a history of adrenal insufficiency are at increased risk for moderate to severe AEs, such as hypotension, which may occur within 1 to 4 hours after CMP-001 injection but may also occur outside this window. These subjects must receive stress dose steroids (eg, 50 mg to 100 mg hydrocortisone or equivalent orally every 8 hours) before and for 24 to 48 hours after each CMP-001 injection.

#### 5.1.2.2. Observation Following CMP-001 Dosing

Subjects must be observed for at least 4 hours following each of the first 6 CMP-001 injections (W1D1 to W6D1). Beginning with the seventh CMP-001 injection (W7D1), the observation period may be reduced to a minimum of 1 hour following CMP-001 injection at the Investigator's discretion based on the AE profile of the individual subject.

#### 5.1.2.3. CMP-001 Injections

##### 5.1.2.3.1. Injectable Tumor Selection

Eligible subjects must have at least 1 accessible lesion amenable to repeated IT injection. Cutaneous, SC, and/or nodal tumors that are visible, palpable, or detectable by ultrasound guidance are acceptable for IT injection. Tumors should be at least 0.5 cm in longest diameter and need not be the largest lesion. The preferred tumor for IT injection is an accessible lesion that is most rapidly progressing in the judgment of the Investigator.

When more than 1 tumor is amenable to IT injection, the Investigator may inject up to 3 tumors per CMP-001 treatment visit. The total dose of CMP-001 may be divided across the

tumors at the Investigator's discretion, and the volume injected into each tumor must be recorded. The same tumor(s) should be injected each week during therapy, if possible. If an injected tumor is clearly decreasing in size and another accessible non-injected tumor is not, then the Investigator may divide the CMP-001 dose between the 2 tumors or switch from injecting the regressing tumor to injecting the non-responding (or growing) tumor. However, there should always be at least 1 target lesion measuring 1 cm or more in diameter that will not be injected for each subject. These lesions not intended for injection may be located in any metastatic site.

Subjects with metastatic disease who have regression of all injectable lesions, or who have an injection site reaction that precludes injection of the tumor, should receive CMP-001 SC near an original tumor (peritumoral) or in the area of the draining lymph nodes (see Appendix G).

#### 5.1.2.3.2. Method of CMP-001 Administration

Topical or local anesthesia may be used at the Investigator's discretion.

Syringe size is at the discretion of the Investigator or qualified designated staff for administering the CMP-001 study drug according to institutional guidelines or standard operating procedures (SOPs). For methods of CMP-001 administration, see Appendix G.

### 5.1.3. Dose Modifications and Management of CMP-001 Associated Adverse Events

Based on earlier studies of CMP-001, CMP-001–associated adverse events such as injection site reactions and flu-like symptoms may occur within hours following CMP-001 injection. Guidance for the observation period following CMP-001 injection is provided in Section 5.1.2.2. CMP-001 is a TLR9 agonist designed to activate pDCs, which secrete IFN and activate other immune cells to produce IFN-associated T helper cell Type 1-promoting cytokines and chemokines. Therefore, it is expected that the AE profile associated with CMP-001 injection may be similar to that observed after systemic administration of IFNs. These AEs may be observed with any injection and could occur outside of the observation window following an injection. More information can be found in the CMP-001 Investigator's Brochure.

The CMP-001 dose should remain unchanged during the study, unless deemed medically necessary by the Investigator after discussion with the Medical Monitor.

If a planned dose cannot be administered on schedule due to a CMP-001 related toxicity, the injection should be delayed until the toxicity has improved or resolved. When nivolumab dosing is held or delayed, CMP-001 dosing must also be held or delayed. If a subject has CMP-001 dosing withheld for more than 3 consecutive doses for any reason during the Q3W dosing period, resumption of treatment must be discussed with the Medical Monitor, otherwise, the subject will be discontinued from study treatment and will have all EOT assessments performed.

If a planned nivolumab dosing is delayed, the CMP-001 dosing may also be delayed.

#### 5.1.3.1. Injection Site Reactions

Injection site inflammation is expected following the second and subsequent injections of CMP-001. If subjects develop inflammation at the injection site, this may be managed using cold compresses and medications for pain and inflammation, such as acetaminophen or non-steroidal anti-inflammatory agents. If, in the Investigator's opinion, a tumor cannot be

injected due to injection site reaction or pain, refer to Section 5.1.2.3.1 on changing the site of injection.

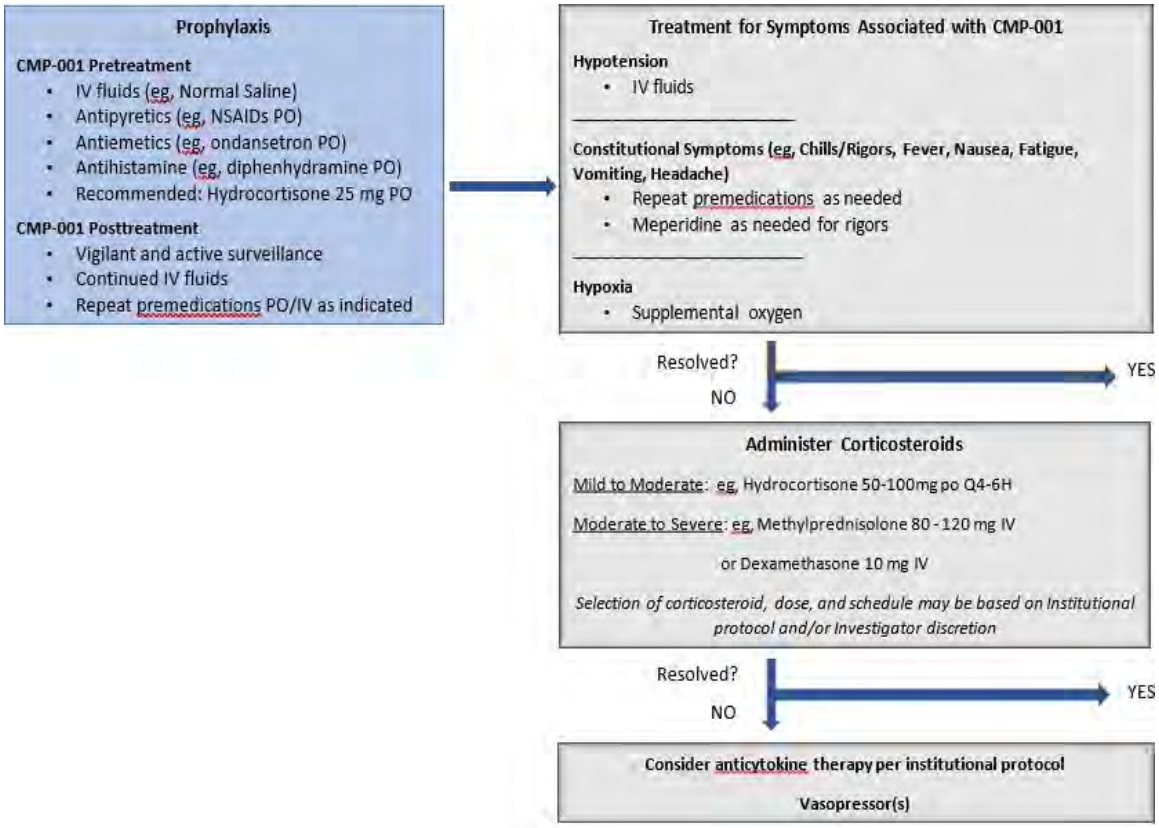
### 5.1.3.2. Management of Adverse Events Associated with CMP-001

CMP-001 has been associated with a variety of flu-like symptoms and hypotension.

These symptoms could include fever, nausea, vomiting, chills, rigors, or hypotension. Additionally, symptoms such as headache, tachycardia, rash, and hypoxia may also occur. Symptoms should be expected within 1 to 4 hours following the injection but may also occur outside this window. Required prophylaxis is outlined in Section 5.1.2.1 to prevent or minimize the severity of these symptoms. If hypotension is unresponsive to IV fluids, stress dose steroids should be administered. The following algorithm (Figure 2) is provided as guidance for the treatment of symptoms associated with CMP-001.

For subjects who experience a Grade 3 or higher symptom deemed related to CMP-001, prophylaxis with stress dose steroids (prednisone 25 mg or equivalent at the Investigator's discretion) is recommended for subsequent CMP-001 doses.

**Figure 2: Suggested Prophylaxis and Treatment for Symptoms Associated with CMP-001**




Abbreviations: IV = intravenously; NSAID = nonsteroidal anti-inflammatory drug; po/PO= orally; Q4-6H = every 4-6 hours.

### 5.1.4. Dose Modifications and Management of Adverse Events Associated with Nivolumab

Nivolumab has been associated with a variety of AEs. The current nivolumab Investigator's Brochure should be consulted for treatment guidance on dose modifications.

If a planned nivolumab dosing is delayed, the CMP-001 dosing may also be delayed. When nivolumab is permanently discontinued because of an immune-related AE, CMP-001 must also be permanently discontinued.

A pattern of immune-related AEs has been defined for nivolumab, for which management algorithms have been developed; these are provided in Appendix H. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.

Nivolumab administration should be delayed or discontinued as specified in Table 2.

**Table 2: Dose Modifications and Management of Adverse Events Associated with Nivolumab**

| Drug-Related Adverse Event | Severity[a] | Action Taken | Clarifications, Exceptions, and Resume Criteria |
|---|---|---|---|
| Colitis or diarrhea | Grade 2 | Delay dose[b] | Dosing may resume when AE resolves to Baseline. |
| | Grade 3 | Delay dose[b] when administered as a single agent | Dosing may resume when AE resolves to Baseline. |
| | Grade 4 | Permanently discontinue | |
| Serum Creatinine Increased | Grade 2 or 3 | Delay dose[b] | Dosing may resume when AE resolves to Grade ≤ 1 or Baseline value. |
| | Grade 4 | Permanently discontinue | |
| Pneumonitis | Grade 2 | Delay dose[b] | Dosing may resume after pneumonitis resolves to Grade ≤ 1 or Baseline value. |
| | Grade 3 or 4 | Permanently discontinue | |
| Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin (T.bili) increased[c] | AST or ALT > 3x and ≤ 5x upper limit of normal (ULN) or T.Bili >1.5 x and ≤ 3 x ULN, regardless of Baseline value | Delay dose[b] | Dosing may resume when laboratory values return to Baseline. |
| | AST or ALT > 5 x ULN or T. bili >3 x ULN, regardless of Baseline value | Delay dose[b] or permanently discontinue (see clarification) | In most cases of AST or ALT > 5 x ULN, study treatment will be permanently discontinued. If the Investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the Investigator and the Medical Monitor/ designee must occur and |

| Drug-Related Adverse Event | Severity[a] | Action Taken | Clarifications, Exceptions, and Resume Criteria |
|---|---|---|---|
| | | | approval from Medical Monitor prior to resuming therapy. |
| Adrenal Insufficiency | Grade 2 adrenal insufficiency | Delay dose[b] | Dosing may resume after adequately controlled with hormone replacement. |
| | Grade 3 or 4 adrenal insufficiency or adrenal crisis | Delay dose[b] or permanently discontinue | Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If adrenal insufficiency resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study drug. |
| Hyperglycemia | Grade 2 or 3 (Hyperglycemia requiring initiation or change in daily management) | Delay dose[b] | Dosing may resume if hyperglycemia resolves to Grade ≤ 1 or Baseline value, or is adequately controlled with glucose-controlling agents. |
| | Grade 4 | Permanently discontinue | Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If hyperglycemia resolves, or is adequately controlled with glucose-controlling agents, participant may not require discontinuation of study drug. |
| Hypophysitis/ Hypopituitarism | Symptomatic Grade 1 to 3 that is also associated with corresponding abnormal lab and/or pituitary scan | Delay dose[b] | Dosing may resume if endocrinopathy resolves to be asymptomatic, or is adequately controlled with only physiologic hormone replacement. |
| | Grade 4 | Delay dose[b] or permanently discontinue | Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study drug. |
| Hyperthyroidism or Hypothyroidism | Grade 2 or 3 | Delay dose[b] | Dosing may resume if endocrinopathy resolves to be asymptomatic, or is adequately controlled with only physiologic hormone replacement or other medical management. |
| | Grade 4 | Delay dose[b] or permanently discontinue | Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement |

| Drug-Related Adverse Event | Severity[a] | Action Taken | Clarifications, Exceptions, and Resume Criteria |
|---|---|---|---|
| | | | or other medical management, participant may not require discontinuation of study drug. |
| Rash | Grade 2 rash covering > 30% body surface area or Grade 3 rash or suspected SJS, TEN, or DRESS | Delay dose[b] | Dosing may resume when rash reduces to ≤ 10% body surface area. Dosing may resume if SJS, TEN, or DRESS is ruled out and rash reduces to is ≤ 10% body surface area. |
| | Grade 4 rash or confirmed SJS, TEN, or DRESS | Permanently discontinue | |
| Guillain-Barre Syndrome (GBS) | Any Grade | Permanently discontinue | |
| Myasthenia Gravis (MG) | Any Grade | Permanently discontinue | |
| Encephalitis | Any Grade encephalitis | Delay dose[b] | After workup for differential diagnosis, (ie, infection, tumor-related), if encephalitis is not drug related, then dosing may resume when AE resolves. |
| | Any Grade drug-related encephalitis | Permanently discontinue | |
| Myelitis | Any Grade myelitis | Delay dose[b] | After workup for differential diagnosis, (ie, infection, tumor-related), if myelitis is not drug related, then dosing may resume when AE resolves. |
| | Any Grade drug-related myelitis | Permanently discontinue | |
| Neurological (other than GBS, MG, encephalitis, or myelitis) | Grade 2 | Delay dose[b] | Dosing may resume when AE resolves to Baseline. |
| | Grade 3 or 4 | Permanently discontinue | |
| Myocarditis | Symptoms induced from mild to moderate activity or exertion | Delay dose[b] | Dosing may resume after myocarditis has resolved. |
| | Severe or life threatening, with symptoms at rest or with minimal activity or exertion, and/or where intervention indicated. | Permanently discontinue | |

| **Drug-Related Adverse Event** | **Severity[a]** | **Action Taken** | **Clarifications, Exceptions, and Resume Criteria** |
|---|---|---|---|
| Pancreatitis:<br>Amylase or Lipase increased | Grade 3 with symptoms | Delay dose[b] | Note: Grade 3 increased amylase or lipase without signs or symptoms of pancreatitis does not require dose delay. Dosing may resume when subject becomes asymptomatic. |
| | Grade 4 | Permanently discontinue | |
| Uveitis | Grade 2 uveitis | Delay dose[b] | Dosing may resume if uveitis responds to topical therapy (eye drops) and after uveitis resolves to Grade ≤ 1 or Baseline. If subject requires oral steroids for uveitis, then permanently discontinue study drug. |
| | Grade 3 or 4 uveitis | Permanently discontinue | |
| Other drug-related AE **(not listed above)** | Grade 2 non-skin AE, except fatigue | Delay dose[b] | Dosing may resume when AE resolves to Grade ≤ 1 or Baseline value. |
| | Grade 3 AE - First occurrence lasting ≤ 7 days | Delay dose[b] | Dosing may resume when AE resolves to Grade ≤ 1 or Baseline value. |
| | Grade 3 AE- First occurrence lasting > 7 days | Permanently discontinue | |
| | Recurrence of Grade 3 AE of any duration | Permanently discontinue | |
| | Grade 4 or Life-threatening adverse reaction | Permanently discontinue | |
| Other drug-related laboratory abnormality **(not listed above)** | Grade 3 | Delay dose[b] | Exceptions:<br>No delay required for: Grade 3 lymphopenia<br>Permanent Discontinuation for: Grade 3 thrombocytopenia > 7 days or associated with bleeding. |
| | Grade 4 | Permanently discontinue | Exceptions: The following events do not require discontinuation of study drug:<br>• Grade 4 neutropenia ≤ 7 days<br>• Grade 4 lymphopenia or leukopenia<br>• Grade 4 isolated electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are responding to supplementation/appropriate |

| Drug-Related Adverse Event | Severity[a] | Action Taken | Clarifications, Exceptions, and Resume Criteria |
|---|---|---|---|
| | | | management within 72 hours of their onset. |
| Hypersensitivity reaction or infusion reaction (**manifested by fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions**) | Grade 3 or 4 | Permanently discontinue | Refer to Section 5.1.4.2. on Treatment of Related Infusion Reactions. |

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; DRESS = drug reaction with eosinophilia and systemic symptoms; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; ULN = upper limit of normal.

a Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0.

b Resume treatment when adverse reaction improves to Grade 0 or 1.

c Resume treatment when AST/ALT returns to Baseline.

Nivolumab dosing should also be delayed for any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, warrants delaying the dose of study medication.

Any event that leads to delay in dosing lasting > 12 weeks from the previous dose requires discontinuation, with the following exceptions:

- Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed.
- Dosing delays lasting > 12 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the Medical Monitor (or designee).

Subjects who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when re-treatment criteria are met (see Section 5.1.4.1). Tumor assessments should continue as per protocol even if dosing is delayed.

A pattern of immune-related AEs has been defined, for which management algorithms have been developed; these are provided in Appendix H. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.

#### 5.1.4.1. Criteria to Resume Nivolumab Treatment

Please see Table 2 for guidance on resuming treatment.

Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

#### 5.1.4.2. Treatment of Nivolumab-Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. Any Grade 3 or 4 infusion reaction should be reported within 24 hours to the study Medical Monitor/designee and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE v5.0 guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

**For Grade 1 symptoms** (mild reaction; infusion interruption not indicated; intervention not indicated):

- Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab administrations.

**For Grade 2 symptoms** (Therapy or infusion interruption indicated but responds promptly to symptomatic treatment [eg, antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, IV fluids]; prophylactic medications indicated for ≤24 hours):

- Stop the study drug infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further study medication will be administered at that visit.
- For future infusions, the following prophylactic premedications are recommended:
  - diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab infusion. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

**For Grade 3 or 4 symptoms** (severe reaction, Grade 3: Prolonged [eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated):

- Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for SC administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. Study drug will be permanently discontinued. Investigators should

follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms.

In case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

#### 5.1.4.3. Nivolumab Treatment Beyond Disease Progression

Reasons for treatment discontinuation are described in Section 4.5. These include discontinuation for progressive disease per RECIST v1.1 and clinical disease progression in the opinion of the Investigator.

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD (Spigel-2017).

Subjects treated with nivolumab will be permitted to continue nivolumab treatment beyond initial RECIST v1.1-defined PD assessed by the Investigator up to a maximum of 24 months from date of first dose as long as they meet the following criteria:

- Investigator-assessed clinical benefit
- Tolerance of study treatment
- Stable performance status

### 5.1.5. Subject Randomization and Stratification

Subjects who complete Screening procedures and meet inclusion/exclusion criteria will be randomized in a 1:1 ratio to Arm A (CMP-001 in combination with nivolumab) or Arm B (nivolumab monotherapy) using an Interactive Web Response System (IWRS) and stratified by the following factors:

- TNM Stage AJCC Cancer Staging Manual Eighth Edition (M0/M1a/M1b versus M1c/M1d)
- Tumor PD-L1 expression (≥ 5% versus < 5%)

During the Screening process, subject-specific values will be recorded for each of the 2 stratification variables. Based on the entered values, the subject will be assigned to a treatment group according to a preprogrammed randomization schedule, which is designed to balance the 2 treatment groups by each variable to the extent possible.

Subjects will be assigned a unique Subject identification (ID) number by the IWRS at randomization. This number will be recorded on the subject's electronic case report from (eCRF) pages and used to identify the subject throughout the study. Once a subject number is assigned, it cannot be reassigned to any other subject.

Details of the IWRS randomization and stratification process will be provided in the Trial Supply Management Manual.

### 5.1.6. Blinding and Unblinding Process

This is an open-label study.

## 5.2. Prior and Concomitant Medications

IMPORTANT: Please refer to Section 5.1.2.1 for required prophylaxis prior to CMP-001 administration. Prophylaxis administered before and after CMP-001 dosing will be collected for each visit.

Please refer to Section 4.4 for prohibited treatments.

Concomitant medications will be assessed continually from 30 days before the first dose of study treatment (W1D1) through 100 days after the last dose of study treatment or until an alternative cancer treatment is initiated, whichever occurs first. Treatment medications for AEs related to study treatment that occur more than 100 days after the last dose of study treatment or until an alternative cancer treatment is initiated, whichever occurs first, will be collected. Subjects who discontinue CMP-001 but remain on treatment with nivolumab will continue to have concomitant medications/treatments collected according the Schedule of Assessments (Table 1).

In addition, at each LTSFU contact, an inquiry will be made regarding the start of any new cancer treatments since the date of the last contact. Prior cancer treatments will be documented on a separate eCRF.

## 5.3. Treatment Compliance

CMP-001 injections must be performed by qualified, trained site personnel. Any deviations in planned dosing will be documented in the source documents, verified by the Clinical Research Associate (CRA), and recorded as a protocol deviation as appropriate. Nivolumab will be administered by trained site personnel at the clinic site according to the dosing instructions provided in the nivolumab Investigator's Brochure and in the Pharmacy Manual.

# 6. STUDY TREATMENT MATERIALS AND MANAGEMENT

## 6.1. Study Treatments

Nivolumab is a Food and Drug Administration (FDA) approved drug product for the treatment of several types of cancer in multiple regions including the United States (Dec-2014), the European Union (Jun-2015), and Japan (Jul-2014). The physical characteristics of nivolumab are found in the nivolumab Investigator's Brochure.

CMP-001 is an investigational study drug and will be provided by the Sponsor. CMP-001 is provided as a 5 mg/mL solution in a single-use vial. Each single use vial will contain either 1.0 mL extractable volume, for a 5 mg dose of CMP-001, or 2.0 mL extractable volume, for a 10 mg dose of CMP-001. The physical characteristics and other details about CMP-001 study drug are found in the CMP-001 Investigator's Brochure and the Pharmacy Manual.

At the end of the treatment period, study treatment will no longer be provided to subjects/Investigators unless the Sponsor chooses to extend the study. The Investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.

## 6.2. Study Drug Labeling and Packaging

Details of the study drug labeling and packaging are provided in the Pharmacy Manual. The study drug vials will be labeled with the following information:

- The protocol number
- The kit number
- Number of vials per kit (carton only)
- The batch number of the drug
- The drug name, concentration, and nominal volume per vial
- The recommended storage conditions of the drug
- Cautionary statement to keep away from children
- Cautionary statement indicating that the drug is for investigational use only
- The name and address of the Sponsor

## 6.3. Study Drug Handling, Storage, Accountability

All study drug vials will be transported, received, stored, and handled in accordance with the carton and vial labels and instructions provided to the site and relevant personnel. The site's SOPs and applicable regulations will be followed.

Appropriate storage and transportation conditions will be maintained for study drug vials from the point of manufacture up to delivery. All shipments of study drug vials will include a temperature monitoring device that records required storage conditions for the vials at regular intervals for the entire time the shipment is in transit.

Upon receipt by the site, the designated site personnel will examine the shipment and temperature monitoring devices to verify the study drug vials were received in acceptable condition. Vials received in acceptable condition should be stored at the specified temperature (2°C to 8°C) in a locked area accessible only to designated site personnel until

dispensed. Dispensed study drug vials will be stored in a limited access area under appropriate environmental conditions as defined in the Pharmacy Manual. Vials not received in acceptable condition should be immediately quarantined at the appropriate temperature (2°C to 8°C), and the site personnel must immediately notify the IQVIA Biotech CRA. Such study drug vials may not be used until IQVIA Biotech representatives (eg, IQVIA Biotech CRA) has conveyed a determination about these specific study drug vials.

The designated site personnel will be responsible for maintaining accurate records of the quantity and dates of all study drug supplies received, dispensed, and returned, in accordance with applicable regulations and the site's SOPs. The quantity of study drug lost, destroyed, or otherwise unaccounted for must also be accounted for and documented.

All original study drug vials, whether empty or containing study drug, will be kept at the site. Study drug vials are single-use only; therefore, contents of partially used study drug vials may not be combined or dispensed again, even to the same subject, nor relabeled or reassigned for use by other subjects. Unused study drug vials will be available for verification by the study monitor. Once dispensed, used study drug vials will be stored in a limited access area under appropriate environmental conditions.

At each investigational site closeout visit and end of clinical trial, a final study drug vial accountability review and reconciliation must be completed by the Sponsor or its representatives and any discrepancies must be investigated, and their resolution documented. All study drug vials will be destroyed at the investigational site as per institutional SOPs after site closeout has been completed or if approved by the Sponsor or its representative as required by the site (ie, space limitations, policy) once drug accountability is conducted by the IQVIA Biotech CRA. A copy of the site destruction SOP must be maintained on file and available for the IQVIA Biotech CRA. If unable to destroy on site, please inform the IQVIA Biotech CRA.

Details of the study drug storage and handling are provided in the Pharmacy Manual.

## 6.4. Study Drug Dispensing

CMP-001 will be dispensed, prepared, and administered according to the Pharmacy Manual and site SOPs. Details regarding the preparation and administration of the CMP-001 is outlined in the Pharmacy Manual. Only eligible subjects participating in the study may receive CMP-001. CMP-001 study drug is dedicated to each study and is labeled specifically for each CMP-001 study. Only authorized and qualified site staff may dispense, prepare, or administer CMP-001.

Nivolumab will be dispensed, prepared, and administered according to the Pharmacy Manual, and site SOPs.

# 7. STUDY ASSESSMENTS AND PROCEDURES

## 7.1. Procedures and Assessments

Assessments to be performed at Screening and throughout the study are specified in the Schedule of Assessments (Table 1).

### 7.1.1. Informed Consent

Subjects must sign a written informed consent form (ICF) prior to the initiation of any study procedures and thereafter if there are any ICF changes. Subjects will be given a signed copy of the ICF to take home. Subjects unable to provide written informed consent on their own behalf will not be eligible for the study.

### 7.1.2. Eligibility Criteria

Subjects must meet all inclusion and exclusion criteria to be eligible for the study. Refer to Section 4.

### 7.1.3. Demographics

Demographic data will be collected during Screening. Demographic data will include date of birth, sex, ethnicity and race (ie, white, black or African American, Asian, American Indian/Alaskan Native, Native Hawaiian/other Pacific Islander, or other).

### 7.1.4. Medical History

At Screening, a general medical history will be obtained, including chronic conditions and comorbidities, relevant acute conditions or infections, surgical procedures unrelated to melanoma, and any reported conditions affecting major body systems during the 10 years prior to Screening.

### 7.1.5. Melanoma History

Eligible subjects must have been diagnosed with histopathologically or cytologically confirmed Stage III or IV metastatic malignant or unresectable melanoma. Subjects with uveal, acral, or mucosal melanoma are not eligible.

At Screening, a detailed melanoma history will be obtained, including date of initial diagnosis, AJCC melanoma cancer staging at diagnosis, and BRAF mutation status including treatment with a kinase inhibitor targeted for BRAF mutation (with or without a MEK inhibitor). BRAF mutation status must be assessed with an FDA-approved test. Sites should refer to the Eighth Edition AJCC Cancer Staging Manual (AJCC-2017) for cancer staging.

PD-L1 status from prior biopsies, if available, will be recorded in the electronic data capture (EDC).

### 7.1.6. Prior Cancer Treatments

Details regarding all prior cancer treatments, including drug generic name, dose (if available), route of administration, start date, end date, best response, and last response to prior therapy, will be documented on a separate page in the EDC. Data on prior surgical procedures related to melanoma will also be captured in the EDC.

### 7.1.7. Medication History

All medications (see Section 5.2) administered to the subject from 30 days prior to first dose of study treatment (W1D1) until 100 days after discontinuation of both CMP-001 and nivolumab will be recorded in the EDC. Treatment medications for AEs related to study treatment that occur more than 100 days after the last dose of study treatment will also be collected. Documentation for each medication will include the generic name of the medication, total daily dose, route of administration, dates of administration, and indication for use. Combination drugs must be listed separately by each component study treatment and dose. Prior cancer treatment will be recorded separately.

### 7.1.8. Physical Examination

Physical examinations, including height and weight, will be conducted as specified in the Schedule of Assessments (Table 1). A full physical examination will be conducted at Screening and EOT. If the Screening full physical examination is performed >72 hours prior to the W1D1 visit, then a brief (symptom directed) physical examination must be performed within 72 hours prior to the first injection of CMP-001. Brief physical examinations focused on areas of disease or AEs may be performed at any clinically indicated time but must be obtained before the first, third, and seventh weekly CMP-001 injections (W1D1, W3D1, W7D1) and at each CMP-001 injection visit thereafter. Height will be obtained at Screening only and weight will be obtained at all physical examination assessments.

### 7.1.9. Vital Signs

Vital signs will be conducted as specified in the Schedule of Assessments (Table 1). Vital signs include measurement of blood pressure (systolic and diastolic blood pressure), respiratory rate, heart rate, and body temperature. Blood pressure and heart rate should be taken in the seated position following ≥3 minutes of rest. When vital signs are scheduled at the same time as collection of a blood sample, the vital sign measurements should be obtained before the scheduled phlebotomy. If a study visit occurs where only nivolumab is administered, vital signs must be collected before the start of the nivolumab infusion. If an indwelling cannula is being used to obtain blood, blood pressure should be measured in the arm opposite to the cannula placement.

### 7.1.10. Eastern Cooperative Oncology Group Performance Status

At Screening, the ECOG performance status (Appendix A) will be assessed and must be either 0 or 1 for the subject to be eligible. The ECOG performance status will be assessed as specified in the Schedule of Assessments (Table 1).

### 7.1.11. Electrocardiogram

A single standard, 12-lead electrocardiogram (ECG) will be obtained as specified in the Schedule of Assessments (Table 1). Assessed ECG parameters will include heart rate and PR, QRS, QT, and QT corrected for heart rate (QTc) intervals. QT will be corrected using Fridericia's (QTcF) formula. ECGs will be performed after the subject has been resting in supine or semi-supine position for at least 5 minutes. When an ECG is scheduled at the same time as a blood sampling, the ECG reading should be obtained before the scheduled blood sampling. The ECG results will be interpreted at the site by a medically qualified person. If indicated, the ECG must be evaluated by a cardiologist or qualified internist.

### 7.1.12. Clinical Laboratory Assessments

Clinical laboratory tests will be performed as specified in the Schedule of Assessments (Table 1). Additional tests may be performed as clinically indicated.

Clinical laboratory parameters (Table 3) to be obtained include:

- Hematology, chemistry, and urinalysis assessments
- Coagulation (PTT, PT, and INR) assessments
- Thyroid function tests (thyroid stimulating hormone, triiodothyronine, and free thyroxine ) for clinical signs and symptoms of thyroid disorder
- Autoimmune panel

A central laboratory will be used for clinical laboratory safety assessments; local laboratories may be used for eligibility and treatment decisions. The central laboratory will provide collection supplies and perform analysis of clinical laboratory evaluations. Specimens will be appropriately processed, and laboratory reports will be provided to the Investigator. A summary of the number and volume of laboratory specimens collected at each study visit is provided in Appendix B.

The Investigator is responsible for reviewing local and central laboratory results and assessing all out-of-range findings as either clinically significant or non-clinically significant. Clinically significant laboratory results should be recorded as medical history if prior to CMP-001 dosing at W1D1 or as AEs following CMP-001 dosing at W1D1 in the eCRF.

**Table 3: Clinical Laboratory Assessments**

| Hematology | Serum Chemistry | Urinalysis | Other Laboratory Tests |
|---|---|---|---|
| Red blood cells (RBCs)<br>White blood cells (WBCs)<br>Differential WBC count<br>Total leukocyte count, including differential<br>Hemoglobin<br>Hematocrit<br>Platelets | Alanine aminotransferase<br>Albumin<br>Alkaline phosphatase<br>Amylase<br>Aspartate aminotransferase<br>Bilirubin<br>Blood urea nitrogen or serum urea<br>Calcium<br>Chloride<br>Creatinine<br>Glucose<br>Lactate dehydrogenase<br>Lipase<br>Phosphorous<br>Potassium<br>Sodium<br>Total protein | Blood<br>Glucose<br>Nitrites<br>pH<br>Protein<br>Specific gravity<br>WBCs<br><br>**Microscopic battery:**<br>RBCs, WBCs, epithelial cells, casts (only if significant positive findings on urinalysis) | **Coagulation:**<br>Partial thromboplastin time<br>Prothrombin time<br>International normalized ratio<br><br>**Thyroid Function Studies:**<br>TSH, T3, free T4 (at Screening)<br>TSH, with reflexive T3 and free T4 if TSH is abnormal (on treatment)<br><br>**Autoimmune laboratory panel:**<br>Anti-doubled stranded DNA, antinuclear antibody, antineutrophil cytoplasmic antibody, rheumatoid factor, and antibodies to ribonucleoprotein<br>HIV<br>Hepatitis B and C |

Abbreviations: RBC = red blood cell; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; WBC = white blood cell.
Note: Refer to the Laboratory Manual for additional information.

### 7.1.13. Pregnancy Testing

Pregnancy testing will be performed on women of childbearing potential at the time points specified in the Schedule of Assessments (Table 1). A central serum pregnancy test is required during Screening. Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) prior to dosing at W1D1 as specified in Table 1. Urine pregnancy testing will be completed for time points after Screening. If a urine pregnancy test is positive at any time point, the test must be confirmed with a serum sample. If a serum pregnancy test is required based on a positive urine pregnancy test, serum test results must be confirmed as negative prior to enrollment or subsequent treatment of the subject.

If the serum test confirms the subject is pregnant, they must have the EOT visit and the pregnancy must be reported.

## 7.2. Disease Assessments

Disease assessments (radiographic, photographic, and CNS imaging) will be collected according to the Schedule of Assessments (Table 1).

Acceptable assessment methods, definition of measurable disease, and selection of target and non-target lesions will be defined by RECIST v1.1 (see Appendix D).

All disease assessments will be evaluated by BICR according to RECIST v1.1, and by Investigator according to RECIST v1.1 (see Appendix D), iRECIST (see Appendix E), and [redacted]

All scans should be performed at least 2 weeks after a previous CMP-001 IT injection to prevent an injection-related pseudoprogression.

All radiographic and photographic images should be uploaded into the imaging portal within 1 week of completion to enable BICR (see imaging guideline).

### 7.2.1. Radiographic Imaging

Contrast-enhanced CT and MRI are the preferred radiographic imaging modalities for disease assessment. Contrast-enhanced CT imaging is required when contraindications are not present. Contrast-enhanced CT assessments may be combined with positron emission tomography (PET) as long as disease status can be thoroughly assessed. Ultrasound imaging [redacted]

Any additional imaging that may demonstrate tumor response or progression (including scans performed at unscheduled time points and/or at an outside institution) should be collected for RECIST v1.1 tumor assessment and submitted for BICR.

### 7.2.2. Photographic Imaging

Digital photographic images of CMP-001 target and non-target skin lesions, including caliper measurements of superficial cutaneous lesions, will be obtained per the time points specified in the Schedule of Assessments (Table 1). Photos should be taken with a digital camera of adequate resolution according to the imaging guideline. To clearly capture the morphology of the tumor, both the skin lesion and the surrounding tissue must be included in the field of view. Each lesion should be clearly labeled with a unique identifier which must be used throughout the trial. A metric ruler must also be included in the photograph field of view as a size reference.

If a CR is observed, sites should continue to obtain confirmation photographs according to the Schedule of Assessments (Table 1).

Refer to the Imaging Guideline for further guidance.

#### 7.2.2.1. Central Nervous System Imaging

Baseline brain imaging by contrast-enhanced CT or MRI (per site local standards) must be provided at Screening. Subsequent brain imaging is only required for subjects with current or prior history of brain metastases or clinical signs or symptoms of CNS disease. The same modality of brain imaging should be utilized throughout the study for an individual subject.

### 7.2.3. On-Treatment Disease Assessment

On-treatment disease assessments will be collected per the time points specified in the Schedule of Assessments (Table 1).

The volume and inflammation from an IT injection of CMP-001 may cause a tumor to transiently enlarge leading to an inaccurate assessment. All scans should be performed predose and at least 2 weeks after a previous CMP-001 IT injection to prevent injection-related pseudoprogression.

#### 7.2.3.1. Disease Assessment Beyond Progressive Disease

Subjects with PD per RECIST v1.1 as determined by Investigator assessment should remain on treatment per Investigator discretion and have a follow-up scan performed at least 4 weeks after the initial date of PD to confirm progression per RECIST v1.1. Subjects who receive study treatment beyond PD per RECIST v1.1 will have subsequent disease assessments evaluated using iRECIST by the Investigator. Disease assessments should continue according to the Schedule of Assessments (Table 1).

#### 7.2.3.2. Confirmation of Response

Subjects with a CR or PR per RECIST v1.1 or iCR or iPR per iRECIST as determined by Investigator assessment must have a confirmatory assessment at least 4 weeks after the initial response. All scans should be performed at least 2 weeks after the previous CMP-001 injection to prevent injection-related pseudoprogression.

Once confirmed, subsequent assessments should continue according to the Schedule of Assessments (Table 1).

## 7.3. Translational Assessments

### 7.3.1. Collection of Blood for Translational Biomarker Analyses

Blood samples, including serum and/or plasma, will be collected for exploratory assessments during the Phase 2 portion of the study as specified in the Schedule of Assessments (Table 1). The procedures for sample collection, processing, storage, and shipment are provided in the Laboratory Manual. Blood samples will be tested to determine concentration of CXCL10 before and during treatment with CMP-001 to evaluate association with the observed clinical responses to study treatment. Samples may be used for additional exploratory analysis of biomarkers thought to play a role in melanoma, cancer immunotherapy, or TLR9, including but not limited to concentration of serum/plasma analytes. These findings may be analyzed for association with observed clinical responses to the combination of CMP-001 and nivolumab and subsequent exploration of factors associated with response or resistance to CMP-001 in combination with nivolumab. These samples may be also used for research to develop methods, assays, prognostics, and/or companion diagnostics related to TLR9 agonism and cancer immunotherapy.

### 7.3.2. Collection of Tumor Biopsies for PD-L1 Staining and Translational Analyses

Determination of PD-L1 expression is required to confirm subject eligibility.

Fresh tumor biopsy samples are mandatory, if safe and medically feasible, as specified in the Schedule of Assessments (Table 1). If in the Investigator's opinion it is unsafe to perform a new biopsy, archival material must be used for analysis of PD-L1 expression. The decision and rationale to forego biopsy samples at Screening or during the treatment period should be clearly documented. Archival tumor biopsy samples should also be collected during Screening, if available.

Tumor biopsies will be used to assess PD-L1 expression and may be used to analyze tumor immune cell infiltrates, such as CD3+CD8+ T cells. Biopsies may be used for additional exploratory analysis of biomarkers thought to play a role in melanoma, cancer immunotherapy, or TLR9, including but not limited to RNA analyses to monitor gene expression and DNA analyses to identify mutations associated with cancer. These findings may be analyzed for association with observed clinical response, resistance, and/or AEs to the combination of CMP-001 and nivolumab.

Additional tumor biopsies may be collected during the study at the discretion of the Investigator.

## 7.4. Safety Assessments

Safety will be assessed on an ongoing basis throughout this study. All safety assessments and AEs will be recorded on the appropriate eCRF and reported to the Sponsor or its representatives (as applicable). All AEs/SAEs will be assessed continually from the time of informed consent through 100 days after the last dose of study treatment (both CMP-001 and nivolumab) or until an alternative cancer treatment is initiated, whichever occurs first, for all subjects. All other medical occurrences (non-adverse events) that begin before the start of study treatment should be recorded on the Medical History/Current Medical Conditions section of the eCRF, not the AE section. All AEs reported on or after the date that study treatment was first administered (W1D1), will be recorded on the eCRF and will be considered treatment-emergent adverse events (TEAEs). All TEAEs, defined as an AE that started or worsened in severity on or after the date that study treatment was first administered (W1D1), will be graded according to CTCAE v5.0 (Appendix C) and coded using Medical Dictionary for Regulatory Activities (MedDRA). Worsening TEAEs (ie, increase to higher severity/grade) should be recorded as new AEs. Ongoing AEs with a decrease in severity/grade do not need to be captured as new AEs. Subjects who discontinue CMP-001 but remain on treatment with nivolumab will continue to have AEs collected according to this schedule until 100 days after the last dose of nivolumab or until an alternative cancer treatment is initiated, whichever occurs first.

Abnormal vital sign measurements, clinical laboratory test results, and/or physical examination findings deemed clinically significant by the Investigator may be repeated, until the value returns to Baseline, within normal limits (WNL), or reaches a clinically stable endpoint, as determined by the Investigator. Any post-Baseline abnormal findings that are considered clinically significant by the Investigator will be recorded on the AE page of the eCRF. The Investigator is responsible for reviewing all clinical laboratory results.

Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug-induced liver enzyme evaluations) will be monitored during the follow-up phase via on-site/local laboratories until all study treatment-related toxicities resolve, return to Baseline, or are deemed irreversible.

If a subject shows cardiac- or pulmonary-related signs (hypoxia, abnormal heart rate, or changes from Baseline) or symptoms (eg, dyspnea, cough, chest pain, fatigue, palpitations), the subject should be immediately evaluated to rule out cardiac or pulmonary toxicity.

Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment.

### 7.4.1. Adverse Events

AEs will be assessed continually from the time that the informed consent is signed through 100 days after the last dose of study treatment (both CMP-001 and nivolumab) or until an alternative cancer treatment is initiated, whichever occurs first, for all subjects. Subjects who discontinue CMP-001 but remain on treatment with nivolumab will continue to have AEs collected according to this schedule until 100 days after the last dose of nivolumab or until an alternative cancer treatment is initiated, whichever occurs first. All AEs from the time that the informed consent is signed will be captured on the eCRF.

Treatment-related SAEs starting more than 100 days after the last dose of study treatment will be recorded on the AE eCRF.

Immune-mediated AEs (IMAEs) are AEs consistent with an immune-mediated mechanism or immune-mediated component for which noninflammatory etiologies (eg, infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the subject's case report form.

See Section 8.3 for a full description of the collection and reporting of AEs during this study.

## 7.5. 100-Day Follow-up Contact

The 100-Day Follow-up contact is a safety follow up that may be conducted in the study clinic or via phone and should occur 100 days (+7) after the EOT or until an alternative cancer treatment is initiated, whichever occurs first. The subject should be questioned for any new AEs, resolution of prior AEs, and use of concomitant medications, including other cancer treatments. No other safety assessments are required unless the Investigator identifies a new safety concern that requires further follow-up.

## 7.6. Post-treatment Follow-up

Subjects who discontinue study treatment and transition into PTFU will continue to have disease assessments collected per the time points specified in the Schedule of Assessments (Table 1). Post-treatment follow-up disease assessments will continue until disease progression, initiation of another cancer treatment, death, loss to follow-up, withdrawal of consent, or End of Clinical Trial.

## 7.7. Long-Term Survival Follow-up

Subjects who discontinue study treatment and PTFU will be contacted by the site according to the Schedule of Assessments (Table 1) for LTSFU, which will continue until death, withdrawal of consent, lost to follow-up, or End of Clinical Trial.

OS is a key endpoint of this study. Post-study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study treatment must continue to be followed for collection of outcome and/or survival follow-up data as required until death or the conclusion of the study.

The Sponsor may request that survival data be collected on all treated subjects outside of the protocol-defined window (Schedule of Assessments, Table 1). At the time of this request,

each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contacts or is lost to follow-up.

# 8. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

## 8.1. Adverse Events

### 8.1.1. Definition of an Adverse Event

An AE is an untoward or medical occurrence associated with the use of study treatment (active or placebo drug, biologic, or device) in clinical investigation subjects, which does not necessarily have a causal relationship with the study treatment. An AE can therefore be any unfavorable and unintended symptom, sign, disease, condition, or test abnormality whether or not considered related to study treatment (Appendix C). Adverse events that do not meet the definition for an SAE are considered non-SAEs.

Adverse events should be recorded upon first occurrence and followed until resolution. A persistent AE is continuous and does not resolve between Q3W dosing visits. The AE is documented only once unless the grade becomes more severe. If the grade becomes more severe, the AE must be reported again with the new grade. Any recurrent AE should be reported as new AE.

Adverse events include:

- Changes in health status described by the subject or signs observed by the Investigator or medical staff.
- Test abnormalities (eg, laboratory tests) that result in an alteration in medical care (diagnostic or therapeutic) and/or are considered clinically significant by the Investigator.

Immune-mediated adverse events are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology, which were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the subject's eCRF.

Every AE must be assessed by the Investigator with regard to whether it is considered immune-mediated. For events that are potentially immune-mediated, additional information will be collected on the subject's eCRF.

Disease progression and associated hospitalization, are not considered AEs or SAEs in this study.

Abnormalities present at Baseline will be recorded as medical history and will only be considered AEs if they reoccur after resolution or worsen during the study.

### 8.1.2. Definition of a Serious Adverse Event

An SAE is any AE that fulfills 1 of the criteria outlined in Table 4.

**Table 4: Criteria for Determination of Serious Adverse Events**

| | |
|---|---|
| Death | An adverse event (AE) that results in death.<br>Note: In this study, deaths due to disease progression are not to be reported as serious adverse events (SAEs). |
| Life-threatening AE | An AE that places the subject, in the view of the Investigator, at immediate risk of death from the AE as it occurred (ie, does not include an AE that had it occurred in a more severe form, might have caused death). |
| Required or prolonged inpatient hospitalization[a] | An AE that results in an initial inpatient hospitalization or prolongs an existing hospitalization of the subject. If a subject is hospitalized as part of the clinical use of the study treatment, a period of normal hospitalization will be outlined in the protocol or by the judgment of the Investigator. Hospitalizations longer than this period will be prolonged hospitalizations. |
| Persistent or significant disability/incapacity | An AE that results in a substantial disruption of a subject's ability to conduct normal life functions. |
| Congenital anomaly/birth defect | A congenital anomaly/birth defect that occurs in the offspring of a subject exposed to the study treatment. |
| Important medical event | An AE which may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above, in the opinion of the Investigator. |

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; SAE = serious adverse event; W1D1 = Week 1 Day 1.

a. Planned hospital admissions or surgical procedures for elective procedures or an illness or disease that existed before the time of consent will not be captured as SAEs. If there was a change in medical condition it may be an SAE.

Appendix C: CTCAE v5.0

Examples of "important medical events" include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as with important medical events described above.

Events that meet SAE criteria must be recorded and reported regardless of expectedness or assessed association with study treatment.

Hospitalization due solely to the progression of underlying melanoma should NOT be reported as an SAE.

### 8.1.3. Definition of a Treatment-Emergent Adverse Event

A TEAE is defined as an AE that started or worsened in severity on or after the date that study treatment was first administered (W1D1) until 100 days after the last dose of study treatment or until an alternative cancer treatment is initiated, whichever occurs first.

### 8.1.4. Definition of a Pretreatment Adverse Event

Pretreatment AEs are AEs that are related to study procedures that occur from the time of informed consent to the first dose of study treatment (W1D1).

## 8.2. Evaluation of Adverse Events and Serious Adverse Events

The Investigator or designee is responsible for making an assessment as to the severity (CTCAE v5.0 Grade), causality/relationship to CMP-001 and to nivolumab separately, and outcome of AEs and SAEs (as defined in Section 8.2.3). Every attempt should be made to provide the causality/relationship at the time at the time of reporting the SAE. In addition, the Investigator or designee must report any actions taken as a result of an AE or SAE separately for CMP-001 and nivolumab.

### 8.2.1. Adverse Event Severity/Grade

For each recorded AE or SAE, the Investigator or designee must provide an assessment of severity/grade using the CTCAE v5.0 (Appendix C).

Note that severity is not the same as "seriousness" (defined in Table 4). Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Worsening of an ongoing TEAE (ie, an increase to higher grade) should be recorded as a new AE. Ongoing AEs that decrease in severity/grade should not be captured as new AEs.

**Table 5: CTCAE Adverse Event Grades**

| Classification | Definition |
|---|---|
| Grade 1 | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated |
| Grade 2 | Moderate; minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living |
| Grade 3 | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limited self-care activities of daily living |
| Grade 4 | Life-threatening consequences: urgent intervention indicated |
| Grade 5 | Death related to adverse event |

Appendix C: CTCAE v5.0

### 8.2.2. Relationship to Study Treatment

For each AE or SAE, the Investigator will determine whether there is a reasonable possibility demonstrated by evidence that suggests a causal relationship between the study treatment and each AE according to the categories provided in Table 6 (See Appendix C). Attribution of AEs will be determined for each of the individual components (CMP-001 and nivolumab) of the study treatment. The Investigator may change their opinion of causality in light of follow-up information; if this occurs, the Investigator must amend the AE or SAE information in the EDC and on the paper SAE form accordingly.

**Table 6: Classification for Adverse Event Causality**

| Classification | Definition |
|---|---|
| Unrelated | There is no suspicion of a causal relationship between exposure to the study treatment regimen and the adverse event (AE); another cause of the AE has been identified, no temporal association with study treatment has been identified, or the study treatment cannot be implicated |
| Possibly related | There is some evidence supporting the possibility of a causal relationship between study treatment regimen exposure and the AE; an alternative explanation (ie, concomitant drug or concomitant disease) is inconclusive, the temporal association with study treatment is reasonable, and the causal relationship cannot be excluded |
| Probably related | An AE that has a timely relationship to the administrative of the investigational drug regimen and follows a known pattern of response, but for which a potential alternative cause may be present |
| Definitely related | There is strong evidence that there is a causal relationship between study treatment regimen and the AE; the AE cannot be reasonably explained by an alternate explanation (ie, concomitant drug or concomitant disease) and the temporal association with study treatment is suggestive of a causal relationship |

Note: CMP-001 and nivolumab must be assessed separately. An AE is considered related to treatment if the attribution is "possibly related", "probably related", or "definitely related."
Appendix C: CTCAE v5.0

Every AE must be assessed by the Investigator with regard to whether it is considered immune-mediated. For events that are potentially immune-mediated, additional information will be collected on the subject's eCRF.

### 8.2.3. Classification of Adverse Event Outcome

Adverse event outcome describes the status of the AE at the last observation. The Investigator will document the outcomes of each AE using the categories provided in Table 7.

**Table 7: Classifications for Adverse Event Outcomes**

| Classification | Definition |
|---|---|
| Fatal | Termination of life as a result of an adverse event (AE) |
| Not recovered/not resolved | Subject has not recuperated, or the AE has not improved |
| Recovered/resolved | Subject has recuperated, the AE resolved, or returned to Baseline status / stabilized |
| Recovered/resolved with sequelae | Adverse event has resolved, but the subject has been left with symptoms or pathology |
| Unknown | Not known, not observed, not recorded, or refused |

Appendix C: CTCAE v5.0

### 8.2.4. Action Taken Related to Study Treatment Administration Regarding the Adverse Event

The Investigator will provide the action taken regarding study treatment separately for CMP-001 and nivolumab in response to the AE. Refer to Section 5.1.3 and Section 5.1.4 for allowed dose modifications of CMP-001 and nivolumab, respectively. Classification for each of the potential actions taken are provided in Table 8.

**Table 8: Classifications for Actions Taken Related to Study Treatment Administration Regarding an Adverse Event**

| Classification | Definition |
|---|---|
| No change | No change in administration of study treatment |
| Study treatment delayed | Temporary delay in administration of the study treatment |
| Study treatment withheld | One or more planned doses of study treatment completely withheld (skipped) |
| Study treatment dose reduced | Study treatment dose reduced from the previous dose level[a] |
| Study treatment permanently withdrawn | Administration of the study treatment terminated (no further dosing) |
| Not applicable | Determination of a value is not relevant in the current context |

[a] The CMP-001 dose should remain unchanged during the study, unless deemed medically necessary by the Investigator after discussion with the Medical Monitor; dose reductions of nivolumab are not allowed.

## 8.3. Procedures for Recording and Reporting Adverse Events

The Investigator is required to report to the Sponsor or its representatives all AEs that occur during the clinical study (Title 21 Code of Federal Regulations [CFR] Part 312.64[b] and International Council for Harmonisation [ICH] E6 entitled “Guideline to Good Clinical Practice”). At each study visit, subjects will be evaluated for new AEs and the status of existing AEs. All AEs/SAEs will be captured from the time of ICF and recorded on the eCRF as AEs. All other medical occurrences (non-adverse events) that begin before start of study treatment should be recorded on the Medical History/Current Medical Conditions section of the eCRF, not the AE section. All AEs reported on or after the date that study treatment was first administered (W1D1), will be recorded on the eCRF and will be considered TEAEs. Treatment-emergent adverse events observed until 100 days after the last dose of study treatment (both CMP-001 and nivolumab) or until an alternative cancer treatment is initiated, whichever occurs first, are to be recorded on the AE page of the eCRF.

The date, time of onset, resolution, determination of seriousness, severity, action taken, outcome and relationship to CMP-001 and nivolumab will be recorded for all AEs. AEs starting more than 100 days after the last dose of study treatment should not be recorded on the AE eCRF unless they are serious and considered to be related to study treatment.

All AEs and SAEs experienced by a subject will be recorded on the appropriate eCRF. In addition, for all SAEs a paper SAE Report Form will be completed and submitted to IQVIA Biotech Safety preferably via email to: Safety-Inbox.Biotech@IQVIA.com or by fax to +1 866 761-1274 as back up within 24 hours of awareness. Information including a detailed description of the event; date and time (24-hour clock) of event onset and resolution; determination of seriousness, severity, corrective treatment, outcome, relationship to the individual components (CMP-001 and nivolumab) of the study treatment; and action taken

regarding the study treatment will be recorded. Vital signs, laboratory results, and other safety assessments noted in Section 7.1 will be recorded as AEs if they are determined to be clinically significant findings in the opinion of the Investigator. When possible, a diagnosis should be recorded as an AE rather than symptoms or isolated laboratory abnormalities related to the diagnosis. A medical or surgical procedure is not an AE; rather the condition leading to the procedure should be recorded as the AE. If the condition is not known, the procedure must be recorded as an AE instead. Similarly, death is not an AE, but is rather the outcome of the AE(s) that resulted in death. If the AE(s) leading to death are not known, then death must be reported as an AE.

### 8.3.1. Reporting Serious Adverse Events

All SAEs and associated source documents must be reported in written or typed English via completion of the eCRF AE page and accompanying paper SAE Report Form to IQVIA Biotech Safety (following the same reporting process outlined in Section 8.3 within 24 hours of first knowledge of the event regardless of relationship to the study procedures or individual study treatments. The paper SAE Report Form should be used to record pertinent information, regarding the SAE. The Investigator is requested to supply as much detailed information as possible regarding the event at the time of the initial report.

SAEs will be collected from the time of informed consent until 100 days after the last dose of study treatment or until an alternative cancer treatment is initiated, whichever occurs first. Any SAE considered to have at least possible relationship to the study treatment and discovered by the Investigator at any time period after EOT should be reported throughout the study period.

If at any time after the subject has completed participation in the study, the Investigator or study staff becomes aware of an SAE that occurred during the study reporting period that they believe is possibly, probably, or definitely related to either study treatment (see Section 8.2.2), then the event and any known details must be reported promptly to the Sponsor or its representatives. The following reporting instructions must be followed.

At minimum, the Investigator will be asked to provide the following information:

- For the initial SAE notification, the Investigator must provide, at a minimum, basic information such as the protocol number, subject's year of birth or age at onset, subject ID number, period of study treatment intake, event term, nature of the event, detailed description of the event, seriousness criteria, causality of the event to CMP-001 and nivolumab separately, and severity.
- In addition, the initial SAE information entered on the eCRF and paper SAE Report Form should include all pertinent known information about the SAE and the affected subject, such as the following: subject sex; description of the AE including reason for assessment as serious, and individual study treatment information including doses, dates of dosing, and action taken with individual study treatments.

Follow-up information must be entered or uploaded into the eCRF system and paper SAE Report Form and sent to IQVIA Biotech Safety (following the same reporting process outlined in Section 8.3.1) within 24 hours of the Investigator's first knowledge of the new information. Follow-up SAE reports may describe the evolution of the reported events and any new assessment of their outcome and/or relationship to individual study treatments. Supporting documentation may be solicited from the site even if the SAE occurred at another

institution. Such documentation may include copies of relevant subject/hospital records, and pathology or autopsy reports. For subject deaths, the cause of death is to be recorded as the SAE term. A death certificate and an autopsy report, if performed, should be submitted.

The Sponsor representative contact information is available for SAE reporting on a 24-hour basis and is reviewed during normal business hours. A paper SAE Report Form should be completed and submitted to IQVIA Biotech Safety within 24 hours of awareness.

### 8.3.2. Reporting Pregnancies

Female subjects or the partners of male subjects who become pregnant within 1 year of their last dose of study treatment will be instructed to notify the Investigator immediately.

If the Investigator learns of a report of pregnancy at any time after the W1D1 visit, the Investigator must complete and submit a paper Pregnancy Report Form and report the pregnancy to the IQVIA Biotech Safety within 24 hours of awareness (following the same reporting process outlined in Section 8.3).

The Investigator will inform the subject that the Sponsor or its representatives is required to gather information regarding the course and outcome of a pregnancy that has occurred after exposure to a study treatment. The progress of the pregnancy must be followed until the outcome of the pregnancy is known (ie, delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, additional follow-up information may be requested.

The Investigator will be asked to obtain follow-up information no later than 2 months after the gestational period to obtain maternal/fetal/neonatal outcome and any other relevant information.

Follow-up information may be requested at additional time points. All study-related contacts involving a known pregnancy should include pregnancy status assessment until pregnancy outcome is known.

Please note that pregnancy in and of itself is not an AE or an SAE. Pregnancy should not be entered into the eCRF as an AE unless the Investigator suspects an interaction between the study treatment and the contraceptive method. Additionally, all information received will be assessed for any AEs and SAEs and processed per study guidelines. If the subject is discontinued because of pregnancy, pregnancy will be documented as the reason for study discontinuation. Spontaneous abortions and stillbirths will be reported as SAEs.

### 8.3.3. Reporting Serious Adverse Events to Institutional Review Boards and Regulatory Authorities

Investigators will follow up on expedited safety reports (unexpected SAEs that are determined to be associated with the use of study treatment) from the Sponsor or its representatives. The Investigator is responsible for fulfilling applicable local reporting requirements to their Institutional Review Board (IRB). Investigators must forward copies of the IRB notification to the Sponsor or its representatives.

In the United States, the Sponsor will be responsible for notifying the FDA of any serious unexpected suspected adverse reaction that is determined to be associated with the use of study treatment. The Sponsor’s assessment of attribution and expectedness will determine regulatory reporting.

### 8.3.4. Follow-up of Adverse Events/Serious Adverse Events

All AEs and SAEs documented at a previous visit that are designated as not recovered/resolved will be reviewed by the Investigator at subsequent visits.

All AEs will be followed until resolution of AE, completion of the subject's study participation, or study termination, whichever occurs first.

Serious AEs and AEs resulting in discontinuation will be followed until 1 of the following occurs:

- The event resolves.
- The event stabilizes.
- The event returns to a Baseline value if a Baseline value is available.
- The event can be attributed to agents other than the study treatment or to factors unrelated to study conduct.
- The Investigator and Medical Monitor agree that follow-up is no longer necessary.

Follow-up reports from the Investigator must be provided via completion of the eCRF AE page and accompanying paper SAE page within 24 hours of the Investigator's first knowledge of the new information. Additional information (ie, hospital records, laboratory, or other diagnostic test results) should be provided if requested and/or indicated. In addition, for SAEs the follow-up information should be added using the same form on which the initial SAE was reported. It should be completed and submitted to IQVIA Biotech Safety via email:

Safety-Inbox.Biotech@IQVIA.com

Rules for AE/SAE follow-up apply to all subjects, including those who withdraw consent prior to study completion (to the extent allowed). The Investigator will ensure that follow-up includes further investigations to elucidate the nature and/or causality of the AE/SAE. These investigations must be consistent with appropriate medical management and subject consent.

Investigators are not obligated to actively seek AEs or SAEs in former study subjects that occur pursuant to the follow-up period. However, if the Investigator or designee learns of any AE or SAE at any time after a subject has been discharged from the study and the event is considered as reasonably related to the study treatment, the Investigator will notify the Sponsor.

# 9. STATISTICAL METHODS

Categorical variables will be summarized as the number and percentage of subjects within each category (with a category for missing data, if applicable). Continuous variables will be presented as number (n), mean, median, standard deviation, and range (minimum and maximum).

Data from all investigational sites will be pooled in the analyses.

A detailed statistical analysis plan (SAP) will be finalized before database lock and will document the analysis methods, data handling procedures, and other statistical analysis issues. Statistical analyses will be performed using SAS® software version 9.4 or higher.

## 9.1. Sample Size Calculation

This study will randomize a total of 450 subjects in the Phase 2 and Phase 3 portions of the study. Subjects who have provided written informed consent at the time the enrollment goal in either phase is reached may complete Screening and be randomized if they meet all eligibility criteria, at the discretion of the Sponsor or its representatives.

Phase 2 Sample Size

A total of 140 subjects will be randomized in a 1:1 ratio to receive either CMP-001 in combination with nivolumab (Arm A) or nivolumab monotherapy (Arm B). A sample size of 140 subjects provides 80% power to detect an absolute treatment difference of 25% with a 2-sided alpha level of 0.05, assuming that the ORR in Arm A is 65% and the ORR in Arm B is 40%. The sample size calculation is performed in PASS-2020 for testing 2 independent proportions using the continuity corrected Z-test with pooled variance.

Phase 2/3 Sample Size

If there is a statistically significant treatment difference at a 2-sided alpha level of 0.05 for the ORR at the end of Phase 2, an additional 310 subjects will be randomized in a 1:1 ratio to receive either CMP-001 in combination with nivolumab (Arm A) or nivolumab monotherapy (Arm B). Combined with the 140 subjects enrolled in Phase 2, this will make up the overall Phase 3 study population sample size of 450 subjects.

The Phase 3 sample size of 450 subjects is calculated to compare the PFS by BICR between the 2 treatment arms at an alpha level of 0.05 (2-sided). The final PFS analysis will be performed when at least 331 PFS events have been observed across the 2 treatment arms (PD by BICR review or death from any cause). With 331 PFS events, the study has 90% power to demonstrate a treatment effect in PFS at a 0.05 alpha level (2-sided) when the true HR is 0.70. The smallest treatment effect that can be detected statistically significant in this study is HR 0.805. The sample size calculation is performed in PASS-2020.

## 9.2. Multiplicity

In order to preserve the family-wise type I error rate of 5% (2-sided), the gatekeeping strategy will be applied.
The 5% (2-sided) alpha is allocated to ORR primary analysis at end of Phase 2. If the treatment effect on ORR at end of Phase 2 is statistically significant at a 2-sided alpha level of 0.05, then enrollment in Phase 3 may be triggered. The 5% (2-sided) alpha will be recycled to the Phase 3 primary analysis of PFS. The detailed testing hierarchy including the secondary endpoints will be pre-specified in the SAP. The overall type I error rate for this study will be strictly controlled at 5% (2-sided).

## 9.3. Analysis Sets

The main analysis sets are defined in this section. The Phase 2 analysis sets apply to subjects who are randomized or treated in the Phase 2 portion of the study. The Phase 3 analysis sets apply to all subjects who are randomized or treated in both the Phase 2 portion and Phase 3 portion of the study. Additional analysis sets may be defined in the SAP.

### 9.3.1. Intent-to-Treat Analysis Set

The Intent-to-Treat (ITT) Analysis Set is defined as all subjects who are randomized.

### 9.3.2. Safety Analysis Set

The Safety Analysis Set is defined as all subjects who receive at least 1 dose of study treatment.

### 9.3.3. Per Protocol Analysis Set

The Per Protocol Analysis Set is defined as all subjects who are randomized and are without major protocol deviations.

### 9.3.4. Pharmacodynamic Analysis Set

The Pharmacodynamic Analysis Set is defined as all subjects who receive at least 1 dose of CMP-001 and have at least 1 measurable sample at Baseline and at least 1 evaluable biomarker sample after CMP-001 administration.

## 9.4. Background Characteristics

### 9.4.1. Disposition

The number and percentage of subjects who screen fail, are randomized in the study, are treated in the study, discontinue study treatment, and who discontinue the study will be summarized by treatment arm. The primary reason for treatment and study discontinuation will also be summarized.

Subject disposition will be presented in a by-subject data listing.

### 9.4.2. Demographics and Other Baseline Characteristics

Demographics and other Baseline characteristics (age, sex, race, ethnicity, body weight, height, and body mass index) will be summarized by treatment arm using descriptive statistics for the ITT Analysis Set and listed by subject.

### 9.4.3. ECOG Performance Status

ECOG data will be presented in a by-subject data listing. Change from Baseline in ECOG Performance Status will be summarized by treatment arm for the ITT Analysis Set.

### 9.4.4. Melanoma History

Melanoma history (time since initial diagnosis, tumor stage, nodal status, and metastatic disease status at time of initial diagnosis), and PD-L1 status will be summarized by treatment arm using descriptive statistics for the ITT Analysis Set and listed by subject.

### 9.4.5. Prior Cancer Treatments

All prior melanoma treatments will be captured in the EDC separately from other prior medications. A summary of the number of prior lines of cancer therapy will be generated for the ITT Analysis Set by treatment arm.

### 9.4.6. Medical and Surgical History

Medical and surgical history will be listed by subject. Medical history will be coded using MedDRA.

### 9.4.7. Protocol Deviations

All protocol deviations will be captured electronically and presented in a by-subject data listing. All deviations will be reviewed on an ongoing basis and classified as major or minor.

### 9.4.8. Prior and Concomitant Medications

Prior medications are those taken within 30 days of the first dose of study treatment and discontinued before the first dose of study treatment.

Concomitant medications will be assessed continually from 30 days before the first dose of study treatment (W1D1) through 100 days after the last dose of study treatment (both CMP-001 and nivolumab) or until an alternative cancer treatment is initiated, whichever occurs first. Treatment medications for AEs related to study treatment that occur more than 100 days after the last dose of study treatment will be collected.

Medications will be coded using the World Health Organization drug dictionary and summarized by treatment arm according to the Anatomical Therapeutic Chemical (ATC) class and preferred term for each dose group for the Safety Analysis Set. Subjects will be counted only once for a given concomitant medication for each ATC class and preferred term in the summary tables.

Concomitant medications will be presented in a by-subject data listing.

## 9.5. Study Treatment Exposure and Compliance

The number of CMP-001 and nivolumab doses received by each subject will be summarized descriptively by treatment arm for the Safety Analysis Set. The duration of each treatment, dose intensity, and relative dose intensity will also be summarized.

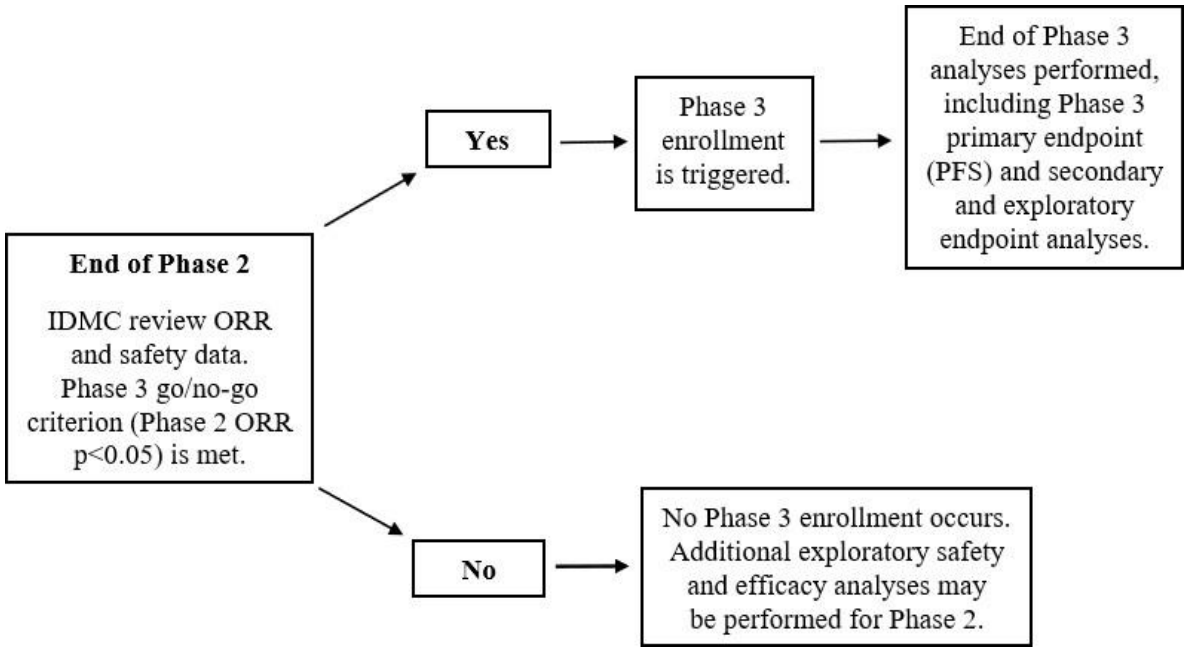
CMP-001 dosing, including date and time of each dose, route of administration, dose administered, location of each injection, and the volume injected into each tumor at each dosing visit will be presented in a by-subject data listing.

Nivolumab dosing, including date, time, and dose administered, will be presented in a by-subject data listing.

## 9.6. Efficacy Analyses

The efficacy analyses will be based on the ITT Analysis Set and may also be performed for the Per-Protocol Analysis Set if deemed appropriate. Phase 3 efficacy analyses will be performed based on the results of the end of Phase 2 primary endpoint results, as described in Figure 3.

**Figure 3: Go/No-Go Decision Tree Based on End of Phase 2 Efficacy**




Abbreviations: IDMC = Independent Data Monitoring Committee; ORR = objective response rate; PFS = progression-free survival.

### 9.6.1. Confirmed Objective Response Rate

The primary efficacy endpoint for the Phase 2 portion of the study is the confirmed ORR based on RECIST v1.1 as determined by BICR.

The confirmed ORR is defined as the proportion of subjects in the analysis set who have confirmed best overall response (BOR) as CR or PR. The confirmed ORR will be calculated as the number of subjects with a confirmed CR or PR divided by the number of subjects in the analysis population [ORR = (confirmed CR + confirmed PR)/# subjects] in each treatment group for the ITT Analysis Set.

ORR will be analyzed using a 2-sided Cochran-Mantel-Haenszel test stratified by stage and PD-L1 expression to compare the 2 treatment arms. Associated odds ratio and 95% CI will also be calculated. Additionally, ORR and the 95% exact CIs will be calculated using the Clopper-Pearson method for each of the 2 treatment arms. The secondary endpoint DCR and the 95% Clopper-Pearson CIs will be summarized as well.

The BOR is defined as the best response designation based on RECIST v1.1 as determined by BICR. Subjects who discontinue due to death due to disease progression, or disease progression, prior to having a post-Baseline tumor assessment will be classified as having a best response of PD. Subjects who discontinue prior to having a post-Baseline scan for other reasons will be counted as non-responders in the ITT analyses.

Objective response rate based on RECIST v1.1 as determined by BICR will be evaluated as a secondary endpoint in the Phase 3 portion of the study. Objective response rate per RECIST v1.1 and iORR per iRECIST by Investigator assessment will also be summarized.

### 9.6.2. Progression-Free Survival

The primary endpoint in the Phase 3 portion of the study, PFS, will be analyzed using a 2-sided log-rank test stratified by stage and PD-L1 expression to compare the 2 treatment arms. All subjects enrolled in the Phase 3 portion of the study (including subjects also treated in Phase 2) will be included in this analysis. HRs and corresponding 2-sided 95% CIs will be estimated using a Cox proportional hazards model, with treatment arm as a single covariate, stratified by the above factors. PFS curves, PFS medians with 95% CIs, and PFS rates at 6 and 12 months with 95% CIs will be estimated using Kaplan-Meier methodology.

PFS is defined as the time from date of randomization to the date of documented progressive disease based on RECIST v1.1 by BICR or death from any cause, whichever occurs first (FDA-2018). Subjects who are alive and progression-free at the time of analyses will be censored in the analyses. Additional censoring rules may be defined in the SAP.

Analysis of PFS and iPFS based on RECIST v1.1 and iRECIST determined by Investigator assessment will also be performed.

### 9.6.3. Overall Survival

Overall survival will be calculated from the date of randomization to death from any cause (FDA-2018). Subjects who are alive at the time of analyses will be censored at the time of last study contact. Median OS will be calculated using the Kaplan-Meier method for each treatment arm OS will be analyzed using the same approach as PFS.

### 9.6.4. Disease Control Rate

The confirmed disease control rate is defined as the proportion of subjects in each treatment arm in the analysis set who have a confirmed best response of CR or PR, or SD lasting at least 4 months. Per RECIST v1.1, CR or PR must be confirmed by a confirmatory assessment performed at least 4 weeks after the initial response. In the case of stable disease, measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks. Disease control rate (DCR) will be analyzed in a similar manner as ORR.

### 9.6.5. Duration of Response

Duration of response (DOR) will be based on RECIST v1.1 as determined by BICR and calculated for responders.

The DOR will be measured from the time at which criteria are first met for CR or PR (whichever is first recorded) until the first date that recurrence or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study). The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented. Censoring details will be described in the SAP, including handling of subjects who continue to be followed for PTFU disease assessments.

Duration of response (DOR) and iDOR will also be determined by Investigator assessment per RECIST and iRECIST.

Duration of response (DOR) will be analyzed using the same approach as PFS.

[redacted]

### 9.6.7. Post-Progression Disease Response

Post-progression disease assessments of tumor response based on iRECIST by Investigator assessment will be summarized for each treatment arm.

[redacted]

## 9.7. Safety Analyses

The assessment of safety will be based on the following assessments: AEs, clinical laboratory tests, vital sign measurements, ECGs, and physical examinations.

### 9.7.1. Adverse Events

Treatment-emergent AEs (TEAEs) will be coded using MedDRA and data will be summarized by treatment arm for the Safety Analysis Set. The number and percent of subjects reporting each TEAE will be summarized, as well as the number of TEAEs. A subject with 2 or more TEAEs within the same level of summarization (ie, system organ class [SOC] or preferred term) will be counted only once in that level using the most severe event or most related (for the relationship to study treatment tables).

Additional summary tables will be generated for Grade 3 or higher TEAEs, TEAEs considered related to treatment (possibly, probably, or definitely), TEAEs by maximum grade and relationship, TEAEs resulting in death, SAEs, related SAEs, and TEAEs leading to treatment discontinuation.

A by-subject AE data listing, including verbatim term, SOC, preferred term, treatment, grade, outcome, and relationship to treatment for CMP-001 and nivolumab, will be generated.

Separate listings will also be generated for Grade ≥3TEAEs , TEAEs considered related to study treatment (possibly, probably, or definitely), TEAEs resulting in death, SAEs, and TEAEs leading to treatment discontinuation.

### 9.7.2. Clinical Laboratory Assessments

Safety central laboratory data will be summarized by treatment arm using descriptive statistics (mean, standard deviation, median, minimum, and maximum), and presented for each time point, including change from Baseline, for the Safety Analysis Set. Shift from Baseline tables will also be created. The categories in the shift tables will be WNL, Low, and High. WNL and Normal will be used when appropriate for urinalysis parameters. Clinically significant post-Baseline laboratory values will be reported as AEs. By-subject data listings of all central laboratory data will be generated and all values outside the normal range will be

flagged as High or Low. Listings of all clinically significant post-Baseline laboratory values from local and central laboratory assessments will be presented in the data listings.

Local laboratory data will be used for subject management including safety reporting and dose selection.

### 9.7.3. Vital Signs

Vital signs will be summarized by treatment arm using descriptive statistics (mean, standard deviation, median, minimum, and maximum) and presented for each time point, including change from Baseline, for the Safety Analysis Set. Clinically significant post-Baseline vital sign findings will be reported as AEs. A by-subject data listing of all vital sign data will be generated.

### 9.7.4. Physical Examinations

Information on the physical examinations will be listed by subject. Clinically significant post-Baseline physical examination findings will be reported as AEs.

### 9.7.5. Electrocardiograms

Heart rate, PR interval, QRS interval, QT interval, and QTcF interval will be summarized using descriptive statistics (mean, standard deviation, median, minimum, and maximum) and presented for each time point, including change from Baseline, by treatment arm for the Safety Analysis Set. Clinically significant post-Baseline ECG findings will be reported as AEs. A by-subject data listing of all ECG data will be generated.

## 9.8. Pharmacodynamic Analyses

Concentrations of CXCL10 and other biomarkers will be summarized by treatment arm using descriptive statistics for all time points for the Pharmacodynamic Analysis Set.

## 9.9. Exploratory Tumor Biopsy Analyses

Tumor biopsy obtained at Baseline and specified time points during the study may be analyzed for protein, RNA, DNA, or other biomarkers related to TLR9, immune checkpoints, and potential markers of resistance or response to immunotherapy for the Pharmacodynamic Analysis Set.

## 9.10. Appropriateness of Measures

The safety assessments in this protocol (ie, physical examination, vital signs, hematology, serum chemistry, urinalysis, coagulation, thyroid function, AEs, and concomitant medications) are widely used and generally recognized as reliable, accurate, and relevant for a late phase oncology study. The safety assessments are adequate to protect the subjects' safety.

### 9.10.1. Blinded Independent Central Review

Blinded Independent Central Review will be used for the primary efficacy assessments of tumor response. The BICR charter will be finalized before the first BICR assessment.

Blinded Independent Central Review Committee responsibilities include confirmation of disease progression prior to study entry.

## 9.11. In-House Blinding

Although this study is being conducted as an open-label study, in order to ensure data integrity, the Sponsor analysis and reporting team will be blinded to subject treatment assignments.

# 10. QUALITY CONTROL AND QUALITY ASSURANCE

## 10.1. Study Monitoring

Before an investigational site can enter a subject into the study, a representative of the Sponsor will determine the adequacy of the clinical facilities and discuss with the Investigator(s) and other site personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the Investigator.

During the study, a monitor from Sponsor or its representatives will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s)
- Confirm that the facilities remain acceptable
- Confirm that the study team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and the study treatment is being properly maintained and accountability records are current
- Perform source data verification with access to all original clinical records for each subject

Additional details regarding monitoring procedures and responsibilities are provided in the Clinical Monitoring Plan.

## 10.2. Case Report Forms

Electronic Case Report Forms will be used in this study. An eCRF is required and should be completed for each screened (ie, subject who has signed an ICF) and enrolled subject. The completed eCRFs are the sole property of Checkmate Pharmaceuticals, Inc. and should not be made available in any form to third parties without written permission from Checkmate Pharmaceuticals, Inc. Limited data will be collected for Screen Failures.

The Investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the eCRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The eCRFs must be electronically signed by the Investigator to attest that the data contained on the eCRF is true. Any corrections to entries made in the source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital’s or physician’s subject chart. In these cases, data collected on the eCRFs must match the data in those charts.

# 11. QUALITY CONTROL AND QUALITY ASSURANCE

## 11.1. Data Quality Assurance

Steps will be taken to ensure the accuracy and reliability of data. Such steps will include the selection of qualified Investigators and appropriate sites, review of protocol procedures with Investigators and associated personnel before study start, and periodic site monitoring visits by the Sponsor or its representatives. Before study initiation, Investigators and site personnel will receive specific training with regards to study procedures and systems as required. Training will include use of clinical laboratory kits and central laboratory operations.

Data management representatives will be available to provide assistance to study center personnel regarding entering subject data. The Sponsor or its representatives will review data contained within eCRFs for accuracy and completeness during remote and/or on-site monitoring visits and after entry into the database. Identified discrepancies will be queried and resolved with the Investigator (or designee) as indicated.

## 11.2. Quality Assurance Audits

To ensure compliance with Good Clinical Practice (GCP) and all applicable regulatory requirements, the Sponsor or its representatives may also conduct a quality assurance audit. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements.

## 11.3. Audits and Inspections by Regulatory Authorities

A regulatory authority or an IRB may visit the site to perform audits or inspections. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

## 11.4. Retention of Records

The Investigator must maintain all documentation relating to the study for a period of 2 years after a marketing application is approved for the test article, or if not approved, or if no application is to be filed, 2 years following the discontinuance of the test article for investigation (21 CFR 312.6I). If it becomes necessary for the Sponsor or a Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

# 12. ETHICS

## 12.1. Ethics Review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or Independent Ethics Committee (IEC) as appropriate. The Investigator must submit written approval to the Sponsor or its representatives before he or she can enroll any subject into the study. Initial IRB approval and all materials approved by the IRB for this study, including the ICF and recruitment materials, must be maintained by the Investigator and made available for inspection.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. No changes will be made in the study without IRB approval, except when required to eliminate apparent immediate hazards to human subjects. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be reapproved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with CMP-001 study treatment. The Sponsor or its representatives will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

Notification of the End of Clinical Trial will be sent to the IRB within 90 days after completion of follow-up for the last subject or per local regulations and guidelines.

In the event the study is ended prematurely, the IRB will be notified within 15 days or per local regulations and guidelines, including the reasons for the premature termination.

The Clinical Study Report will be sent to the sites and IRB where appropriate per local regulations and guidance, within 1 year after the End of Clinical Trial.

## 12.2. Ethical Conduct of the Study

This study will be conducted in compliance with the protocol and in accordance with current US FDA regulations. This study is also designed to comply with ICH E6 Guideline for GCP (CPMP/ICH/135/95), the European Union Clinical Trials Directive 2001/20/EC, as well as the ethical principles that have their origin in the Declaration of Helsinki, adopted by the 18$^{th}$ World Medical Assembly Helsinki, Finland, June 1964 and subsequent amendments.

## 12.3. Written Informed Consent

The ICF should be written in accordance with the current revision of the Declaration of Helsinki and current ICH and GCP guidelines. The Sponsor or its representatives will provide template ICF to the Investigator. The final ICF must be approved by the Sponsor or its representatives prior to being reviewed and approved by the IRB. The final IRB approved ICF must be provided to the Sponsor or its representatives for regulatory purposes.

The Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject

should be given the opportunity to ask questions and allowed time to consider the information provided.

Each subject must provide voluntary written informed consent (and sign other locally required documents) according to local requirements after the nature of the study has been fully explained. Each subject must sign an ICF before any study-related activities are performed and before participation in the study. A copy of the signed ICF must be provided to the subject, and the original signed ICF must remain in each subject's study file and must be available for verification by the study monitor at any time. The Investigator will also ensure each subject follows the proper re-consenting procedures for all applicable or additional versions of the ICF that become effective while they are enrolled in the study.

# 13. PUBLICATION POLICY

All information concerning CMP-001, Sponsor operations, patent application, formulas, manufacturing processes, basic scientific data, and formulation information, supplied by the Sponsor or its representatives to the Investigator and not previously published, is confidential and remains the sole property of the Sponsor. The Investigator agrees to use this information only to complete this study and not for other purposes without the Sponsor's written consent.

The institution and Investigator understand that the information developed in this study will be used by the Sponsor in connection with the continued development of CMP-001, and thus may be disclosed as required to other Investigators, government regulatory agencies, or other scientific groups. To permit the information derived from this study to be used, the Investigator is obligated to provide the Sponsor with all data obtained in the study.

# 14. LIST OF REFERENCES

Ahmed FS, Dercle L, Goldmacher GV, et al. Comparing RECIST 1.1 and iRECIST in advanced melanoma patients treated with pembrolizumab in a phase II clinical trial. Eur Radiol. 2020 Sep 30; online ahead of print.

AJCC Cancer Staging Manual (8th edition). Springer International Publishing: American Joint Commission on Cancer. 2017.

Appay V, Jandus C, Voelter V, et al. New generation vaccine induces effective melanoma-specific $CD8^+$ T cells in the circulation but not in the tumor site. J Immunol. 2006;177(3):1670-1678.

Brahmer J, et al. Five-year follow-up from the CA209-003 study of nivolumab in previously treated advanced non-small cell lung cancer: clinical characteristics of long-term survivors. Oral presentation presented at: American Association for Cancer Research (AACR) Annual Meeting.,; Washington, DC, USA. 2017 April 1-5.

Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity. 2013;39(1):1-10.

Common Terminology Criteria for Adverse Events (CTCAE) v5.0; https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf. Publish date Version 5.0 2017 November 27.

Davar D, Karunamurthy A, Hartman D, et al. Phase II trial of neoadjuvant nivolumab (Nivo) and intra-tumoral (IT) CMP-001 in high-risk resectable melanoma (Neo-C-Nivo): final results. Presented at: Society for Immunotherapy of Cancer 2020 Virtual Meeting. 2020 November 10-15.

Demoulin S, Herfs M, Delvenne P, Hubert P. Tumor microenvironment converts plasmacytoid dendritic cells into immunosuppressive/tolerogenic cells: insight into the molecular mechanisms. J Leukoc Biol. 2013;93:343-352.

Duraiswamy J, Freeman GJ, Coukos G. Therapeutic PD-1 pathway blockade augments with other modalities of immunotherapy T-cell function to prevent immune decline in ovarian cancer. Cancer Res. 2013;73(23):6900-12.

Food and Drug Administration (FDA). Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. 2018. Available from: https://www.fda.gov/media/71195/download.

Felip E, et al. Three-year follow-up from Checkmate 017/057: Nivolumab versus docetaxel in patients with previously treated advanced non-small lung cancer (NSCLC). Poster discussion presentation at the European Society of Medical Oncology Annual Meeting. 2017 Sep 8-12; Madrid, Spain. Poster 1301PD

Fourcade J, Sun Z, Pagliano O, et al. PD-1 and Tim-3 regulate the expansion of tumor antigen-specific $CD8^+$ T cells induced by melanoma vaccines. Cancer Res. 2014;74(4):1045-55.

Goldmacher GV, Khilnani AD, Andtbacka RHI, et al. Response Criteria for Intratumoral Immunotherapy in Solid Tumors: itRECIST. J Clin Oncol. 2020;38(23):2667-2676.

Heckelsmiller K, Rall K, Beck S, et al. Peritumoral CpG DNA elicits a coordinated response of CD8 T cells and innate effectors to cure established tumors in a murine colon carcinoma model. J Immunol. 2002;169:3892–3899.

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2). Available from: https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf

KEYTRUDA® United States Prescribing Information: Merck & Co., Inc. Available from:https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125514s066lbl.pdf.

Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med. 2019;381(16):1535-1546.

Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014;124(2):188-195.

Lemke-Miltner CD, Blackwell SE, Yin C, et al. Antibody opsonization of a TRL9 agonist-containing virus-like particle enhances in situ immunization. J Immunol. 2020;204(5):1386-1394.

Lombardi VC, Khaiboullina SF, Rizvanov AA. Plasmacytoid dendritic cells, a role in neoplastic prevention and progression. Eur J Clin Invest. 2015;45 Suppl 1:1-8.

Milhem M, Zakharia Y, Davar D, et al. Intratumoral injection of CMP-001, a Toll-like receptor 9 (TLR9) agonist, in combination with pembrolizumab reversed programmed death receptor 1 (PD-1) blockade resistance in advanced melanoma. Presented at: Society for Immunotherapy of Cancer 2020 Virtual Meeting. 2020 November 10-15.

Mangsbo SM, Sandin LC, Anger K, Korman AJ, Loskog A, Tötterman TH. Enhanced tumor eradication by combining CTLA-4 or PD-1 blockade with CpG therapy. J Immunother. 2010;33(3):225-235.

NCCN Clinical Practice Guidelines in Oncology. National Comprehensive Cancer Network (NCCN). Cutaneous Melanoma. Version 1 2020.

Nivolumab (OPDIVO, BMS-936558) Investigator's Brochure version 19, dated 29 June 2020 and Addendum No. 01 to Investigator Brochure Version 19, dated 29 June 2020. Bristol-Myers Squibb Company. Princeton, NJ USA.

Oken M, Creech RH, Tormey DC, et al. Toxicity and response criteria of the eastern cooperative oncology group. Am J Clin Oncol. (CCT) 1982; 5:649-655.

OPDIVO™ Annex I Summary of Product Characteristics. Bristol-Myers Squibb Company. 2020.

Power Analysis & Sample Size (PASS) software. Version 20.0.1. NCSS; 2020.

Schadendorf D, Wolchok, JD, Hodi, FS, et al. Efficacy and Safety Outcomes in Patients With Advanced Melanoma Who Discontinued Treatment With Nivolumab and Ipilimumab Because of Adverse Events: A Pooled Analysis of Randomized Phase II and III Trials. J Clin Oncol. 2017;35(34): 3807-3814.

Schadendorf D, Hodi FS, Robert C, et al. Pooled Analysis of Long-Term Survival Data from Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma. J Clin Oncol. 2015;33(17): 1889-1894.

Shirota Y, Shirota H, Klinman DM. Intratumoral injection of CpG oligonucleotides induces the differentiation and reduces the immunosuppressive activity of myeloid-derived suppressor cells. J Immunol. 2012 Feb 15;188(4):1592-1599.

Spigel DR, et al. Randomized results of continuous vs 1-year fixed-duration in patients with advanced non-small cell lung cancer. Oral presentation at the European Society of Medical Oncology Annual Meeting. 2017 Sep 8-12; Madrid, Spain.

Swiecki M, Colonna M. The multifaceted biology of plasmacytoid dendritic cells. Nat Rev Immunol. 2015;15(8):471-485.

Wang S, Campos J, Gallotta M, Gong M, Crain C, Naik E, et al. Intratumoral injection of a CpG oligonucleotide reverts resistance to PD-1 blockade by expanding multifunctional $CD8^+$ T cells. Proc Natl Acad Sci U S A. 2016;113(46):E7240-E7249.

# 15. APPENDICES

# APPENDIX A. ECOG PERFORMANCE STATUS

| Grade | Eastern Cooperative Oncology Group (ECOG)[a] |
|---|---|
| 0 | Fully active, able to carry on all predisease-performance without restriction. |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work. |
| 2 | Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| 3 | Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours. |
| 4 | Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair. |
| 5 | Death |

[a] Oken-1982

# APPENDIX B. APPROXIMATE MAXIMUM AMOUNT OF BLOOD DRAWN FOR ONE YEAR OF STUDY PARTICIPATION

| **Study Phase** | **Estimated Blood Volume** |
|---|---|
| Screening/Baseline | 35 mL |
| Weekly Dosing<br>(7 doses every week) | 245 mL |
| Q3 Week Visits<br>(~15 visits over 1 year) | 375 mL |
| End of Treatment | 35 mL |
| Total Blood Volume Estimate for 1 year of study participation | 690 mL<br>(approximately 2.9 cups) |

# APPENDIX C. COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE) VERSION 5.0

**Common Terminology Criteria for Adverse Events Terms**

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE version 5.0 term is a MedDRA Lowest Level Term.

**Definitions**

A brief definition is provided to clarify the meaning of each AE term. A single dash (-) indicates a definition is not available. Grade refers to the severity of the AE. The CTCAE displays Grade 1 to Grade 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- **Grade 1** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2** Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
- **Grade 3** Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting selfcare ADL**.
- **Grade 4** Life-threatening consequences; urgent intervention indicated.
- **Grade 5** Death related to AE.

A Semi-colon indicates “or” within the description of the grade.
A single dash (-) indicates a grade is not available. Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than 5options for Grade selection.

**Activities of Daily Living (ADL)**

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Selfcare ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

*Version 5.0 Publish date 27 November 2017 (v5.0: 27 November 2017)
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

# APPENDIX D. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) VERSION 1.1

Response criteria were adapted from: RECIST Criteria; Version 1.1, 2009 (http://www.eortc.be/Recist/documents/RECISTGuidelines.pdf). These criteria are provided as reference; any discrepancy should be resolved by consulting the original publication.

**Assessment of Overall Tumor Burden and Measurable Disease**

To assess objective response, it is necessary to estimate the overall tumor burden at Baseline and use this as a comparator for subsequent measurements. Only subjects with measurable disease at Baseline should be included in protocols where objective tumor response is an endpoint. Measurable disease is defined by the presence of at least 1 measurable lesion.

A measurable lesion is defined as one that can be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 1 cm by CT scan (CT scan slice thickness no greater than 0.5 cm)
- 1 cm caliper measurement by clinical examination (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 2 cm by chest x-ray

Non-measurable lesions are defined as all other lesions, included small lesions (longest diameter <1.0 cm or pathological lymph nodes with ≥10 to <1.5 cm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

**Special considerations regarding lesion measurability:**

**Bone lesions:**

Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions. Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as contrast-enhanced CT or MRI can be conserved as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.

**Cystic lesions:**

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

**Lesions with prior local treatment:**

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated

progression in the lesion.

**Baseline Documentation of Target and Non-Target Lesions**

Baseline documentation of tumor sites may include imaging assessment of disease in the chest, abdomen, and pelvis. A Baseline CNS image is required for all subjects within 3 months of Screening. All Baseline tumor measurements must be documented within 4 weeks prior to start of therapy.

**Target Lesions**

All measurable lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at Baseline (this means in instances where subjects have only 1 or 2 organ sites involved a maximum of 2 and 4 lesions respectively will be recorded). Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion that can be measured reproducibility should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the Baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The Baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

**Non-Target Lesions**

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at Baseline. Measurements are not required, and these lesions should be followed as ‘present,’ ‘absent,’ or in rare cases ‘unequivocal progression.’ In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (ie, ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

**Tumor Response Criteria**

**Evaluation of Target Lesions**

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 1 cm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the Baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the Baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 0.5 cm (Note: the appearance of 1 or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

**Evaluation of Non-Target Lesions**

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 1 cm short axis).

Non-complete response/Non-progressive disease: Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of 1 or more new lesions is also considered progression).

**Evaluation of Best Overall Response**

The BOR recorded from the start of the study treatment until the End of Clinical Trial taking into account any requirement for confirmation. The subject's BOR assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. In non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'BOR.'

**Determination of Tumor Response**

| Target Lesions | Non-Target Lesions | New Lesions | Response Assessment |
|---|---|---|---|
| CR | CR | No | CR |
| CR | Non-CR/Non-PD | No | PR |
| CR | Not Evaluated | No | PR |
| PR | Non-PD or Not All Evaluated | No | PR |
| SD | Non-PD or Not All Evaluated | No | SD |
| Not All Evaluated | Non-PD | No | NE |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = inevaluable.

Note: Subjects with a global deterioration of health status, requiring discontinuation of treatment without objective evidence of disease progression at that time, should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression, even after discontinuation of treatment. Conditions that may define "early progression, early death, and inevaluability" are study-specific and should be clearly defined in each protocol (depending on treatment duration and treatment periodicity). In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspiration/biopsy) before confirming the CR status.

**Best Overall Response When Confirmation of CR or PR Are Required**

When confirmation of response is required, complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later).

**Confirmation of CR and PR**

| Overall Response First Time Point | Overall Response Subsequent Time Point | BEST Overall Response |
|---|---|---|
| CR | CR | CR |
| CR | PR | SD, PD, or PRa |
| CR | SD | SD provided minimum criteria for SD duration met, otherwise PD |
| CR | PD | SD provided minimum criteria for SD duration met, otherwise PD |
| CR | NE | SD provided minimum criteria for SD duration met, otherwise NE |
| PR | CR | PR |
| PR | PR | PR |
| PR | SD | SD |
| PR | PD | SD provided minimum criteria for SD duration met, otherwise PD |
| PR | NE | SD provided minimum criteria for SD duration met, otherwise NE |
| NE | NE | NE |

Abbreviations: CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = inevaluable

[a] If a CR is truly met at the first time point, any disease seen at a subsequent time point, even disease meeting PR criteria relative to Baseline, makes the disease PD at that time point (because disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, "CR" may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response PR.

**Guidelines for Evaluation of Measurable Disease**

All measurements should be recorded in metric notation using a ruler or calipers. All Baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of treatment.

Note: Tumor lesions in a previously irradiated area are not optimally considered measurable disease. If the Investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at Baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

Clinical lesions will only be considered measurable when they are superficial and 1 cm diameter as assessed using calipers (ie, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested.

For chest lesions, chest CT is preferred over chest x-ray, particularly when progression is an important endpoint, since CT is more sensitive than x-ray, particularly in identifying new lesions. However, lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

Cross Sectional Imaging: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 0.5 cm or less. When

CT scans have slice thickness greater than 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (ie, for body scans).

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by contrast-enhanced CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

**Duration of Overall Response**

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study). The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

**Duration of Stable Disease**

Stable disease (SD) is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest sum on study (if the Baseline sum is the smallest, this is the reference for calculation of PD).

**Time to Disease Progression**

Defined as the time from the date of first day of enrollment to progression as assessed by the conventional response criteria, death, or the start of further antitumor therapy. Subjects lost to follow-up will be censored at their last known alive date.

# APPENDIX E. IMMUNOTHERAPY RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (IRECIST)

Response criteria were adapted from: Response Evaluation Criteria in Solid Tumors (RECIST) for use in trials testing immunotherapeutics; published in final edited form as: Lancet Oncol. 2017 March; 18(3): e143–e152. doi:10.1016/S1470-2045(17)30074-8. These criteria are provided as reference; any discrepancy should be resolved by consulting the original publication.

**iRECIST**

The basic principles of defining tumor lesions as measurable or non-measurable and assessing tumor responses used in iRECIST remain unchanged from RECIST v1.1. The most important change is in the introduction of an additional follow-up to confirm or withdraw an 'unconfirmed' tumor progression after initial increase in size. Similar to RECIST v1.1, iRECIST is primarily based on the use of contrast-enhanced CT and MRI, while inclusion of clinically visible superficial lesions in malignant melanoma is possible as well.

**Baseline Evaluation**

At Baseline, iRECIST is used similarly to RECIST v1.1 to determine the total tumor burden by defining target and non-target lesions. For that purpose, a distinction is made between measurable and non-measurable lesions (target lesions and non-target lesions).

**Target Lesions**

All measurable solid tumor manifestations with a minimum long axis diameter (LAD) ≥10 mm (or at least double slice thickness), nodal lesions with a short axis diameter (SAD) ≥15 mm and clinical measurements of superficially localized tumor lesions ≥ 10 mm (documented photographically using a tape measure) can be defined as target lesions.

Of these potential target lesions, analogous to RECIST v1.1, up to 5 lesions per subject, can be determined within iRECIST, of which a maximum of 2 lesions per organ can be defined as target lesions. Paired organs, such as lung or kidneys, and organ systems, such as the skeletal or lymphatic systems, are understood as an organ group for which a maximum of 2 target lesions can be defined. The individual quantitative measurement results of the selected target lesions are noted and documented as a Baseline target sum. This Baseline sum diameters are used as reference to further characterize any objective tumor regression or progression in the measurable dimension of the disease.

**Non-Target Lesions**

Non-target lesions are lesions that may not be measured with a sufficient amount of reproducibility, eg, solid tumor lesions <10 mm, lymph node metastases with a SAD ranging between 10 and 14 mm and tumor manifestations without clear borders like infiltrative organ metastases, lymphangitis carcinomatosa, or lesions with highly variable distribution patterns, such as malignant pleural and pericardial effusion or ascites. In addition to these non-target lesions, all other potential measurable target lesions that have not been selected for the category target lesion are also added to the non-target lesion category.

Several tumor lesions of one organ could be combined into one organ group, such as 'multiple lung metastases' or 'diffuse liver metastasis.' Non-target lesions are qualitatively documented as 'present' and do not require a specific indication of quantitative size or

absolute number. This procedure is intended to warrant complete lesion documentation in case of uncountable metastases.

**Bone and Cystic Lesions**

According to RECIST v1.1, there are specific recommendations regarding bone lesions, cystic lesions, and lesions previously treated with local therapy. First, osteolytic bone lesions or mixed lytic-blastic lesions with a measurable soft tissue component ≥10 mm could be considered as target lesions. However, osteoblastic bone lesions represent non-target lesions. Second, cystic metastatic lesions ≥10 mm could be considered as target lesions. However, if non-cystic target lesions are present in the same subject, these should be preferred. Finally, lesions with prior local treatment, eg, radiation therapy or biopsy, should usually not be considered as target lesions unless there has been demonstrated clear tumor progression afterwards.

**Follow-up**

Regular follow-up response assessment every 6 to 12 weeks is recommended for iRECIST. During iRECIST follow-up monitoring, in line with RECIST v1.1, all target lesions defined at Baseline must be quantitatively remeasured and all non-target lesions must be qualitatively re-evaluated. The measurement of the maximum diameter of the target lesion at the new follow-up is independent of the previous direction of the measurement within the lesion or slice position, but always in identical slice orientation. In case a target lesion is reported as too small to measure but still visible, a default value of 5 mm could be used. In the rare case if a target lesion splits into 2 separate lesions, the separate measurements of the lesions should be added together for the target lesion sum. In case target lesions coalesce and are radiologically no longer separable, the maximum longest diameter for the coalesced lesion should be provided and the other lesion should be noted with 0 mm. Lymph node metastases are handled specifically. Even under a highly effective treatment in most cases they will never fully disappear and will only shrink to their physiological size. Lymph nodes are considered as tumor free once their SAD is <10 mm, but the measurements should be recorded in all subsequent follow-ups in order not to overstate progression in case of a minor increase in size, eg, from 9 mm to 11 mm. This means that when lymph node metastases are target lesions, the tumor burden will mostly not become ‘zero’ even in the case of a CR. Please notice that a target lesion defined at Baseline assessment always remains a target lesion, even if it shows a size reduction to less than 10 mm. Similarly, non-target lesions yielding a size increase of more than 10 mm at follow-up remains a non-target lesion but could qualify for ‘unequivocal progression’ in case of an overall level of substantial worsening in non-target disease.

With regards to the measurable target lesion, the proportional change of the sum of the target lesions can be calculated with the formula: Change in (%) = ([∑Follow-up - ∑Baseline/ ∑Nadir]/ ∑Baseline/ ∑Nadir) * 100. Taking as reference the smallest target sum in the study, so called Nadir, which could be the Baseline target sum if that is the smallest sum in the study.

Non-target lesions are assessed qualitatively, ie, visually, as either ‘present,’ ‘disappeared,’ or ‘unequivocal progression.’ When considering determining an ‘unequivocal progression’ of non-target lesions, the total tumor load should always be taken into account in proportion and carefully weighed, as this would necessarily imply classification of ‘PD,’ even if all other lesions have responded strongly or even completely. In case of doubt, the responsible oncologist should be consulted.

In contrast to RECIST v1.1, where new tumor lesions are considered qualitatively and directly denote 'PD' and end of study, within iRECIST, they are differentiated into new measurable and non-measurable lesions. Although new tumor lesions within iRECIST will also be classified as tumor progression, this progression initially counts as an immune unconfirmed progressive disease (iUPD), which should be re-assessed in a dedicated earlier follow-up after 4 to 8 weeks. For classification as new measurable or non-measurable tumor lesions, criteria applied are the same as for the Baseline examination with a maximum of 5 measurable new target lesions per subject and 2 per organ, respectively, which are measured as a separate group at the time of the first occurrence while the sum product of all new measurable target lesions is determined. The new non-measurable lesions are documented qualitatively similarly to the non-target lesions at Baseline. Tumor lesions diagnosed for the first time in a previously unexamined body region are also classified as 'new lesions' in line with RECIST v1.1. The rationale behind this procedure is that the extension of imaging to a previously unexamined region, which leads to the detection of new tumor lesions, is usually triggered by the occurrence of new clinical symptoms.

In case of a new unclear lesion, eg, because of its small size, this lesion should be preferably noted as a 'finding,' therapy should be continued, and follow-up evaluation could clarify if it represents truly new disease. If repeat examination confirms a new tumor lesion, then progression should be declared using the date of the initial scan when the lesion was first detected.

**Tumor Response Criteria**

The overall response according to iRECIST results from the combination of changes in target lesions and non-target lesions, as well as the possible detection and change of new measurable and non-measurable tumor lesions. The objective response in the context of immunotherapy (with the prefix 'i' for immune-related) is differentiated into:

- Immune complete response, which describes the complete disappearance of target lesions and non-target lesion. All lymph nodes must be non-pathological in size (<10 mm in SAD).
- Immune partial response, which occurs when the tumor load of the target lesion is reduced by ≥30% compared to the Baseline, or in the case of complete remission of the target lesion, when 1 or more non-target lesion can still be distinguished.
- Immune stable disease (iSD), which is to be determined if the criteria of iCR or iPR are not met and no tumor progression is present.

In case of a tumor progression, and in order to facilitate differentiation of true tumor progression from pseudoprogression in clinically stable subjects, iRECIST proposes to determine first:

- Unconfirmed progressive disease due to an increase in the sum of all target lesions by ≥20% (but at least ≥5 mm) compared to the time point with the lowest target lesion sum (nadir), or an unequivocal progression of non-target lesions, or by the occurrence of new measurable and/or non-measurable tumor lesions.
- This initially unconfirmed tumor progression might be confirmed by a subsequent follow-up where:
    - Immune confirmed progressive disease is present if further progress of the target sum (≥ 5mm), or any further progress of the non-target lesion,

and/or progress of the new measurable and not measurable lesions either in number or in size (sum ≥ 5mm).

In case of iUPD, the follow-up for re-evaluation and diagnosis of potential pseudoprogression should be carried out earlier, after 4 to 8 weeks, in contrast to the regularly recommended time interval of 6 to 12 weeks. In case tumor progression is not confirmed and target lesions, non-target lesions, and new lesions remain unchanged, iUPD status should be kept and subsequent follow-up should be performed according to the regular schedule, eg, after 8, 16, and 24 weeks. Moreover, if the tumor burden decreases more than 20%, this should be considered iSD; if it decreases more than 30%, this should be considered iPR. If tumor lesions completely disappear, there is iCR even after iUPD.

However, in iRECIST it is clearly recommended to carefully consider the continuation of immunotherapy at the first stage of iUPD. This decision should be thoroughly discussed with both subject and referring physicians and made only in case of subjective stable tumor disease or clinically suspected pseudoprogression. New lesions in a potentially curative therapy approach could be biopsied in order to enable a more reliable differentiation of rare pseudoprogression from more frequent PD and to be able to initiate an early modification of the tumor therapy before the subject may no longer tolerate it due to a physical deterioration. In the case that a biopsy is not technically feasible or only feasible with a significantly increased risk, the confirmation of the less probable delayed therapy response can be represented by a follow-up after 4 to 8 weeks in subjectively stable tumor subjects during this period.

According to RECIST v1.1, the RECIST working group did not believe that there was sufficient data available to recommend implementation of metabolic and/or functional imaging response parameters. An exception is the use of fluorodeoxyglucose PET imaging as an adjunct to determination of progression if a positive fluorodeoxyglucose PET at follow-up corresponds to a new site of disease confirmed by CT. However, the actual literature does not support the non-invasive differentiation of true progression from pseudoprogression by PET/CT.

**Evaluation of Best Overall Response**

For iRECIST, the BOR is the best time point response recorded from the start of immunotherapy until the end of treatment. Immune UPD will not override a subsequent BOR of iSD, iPR, or iCR.

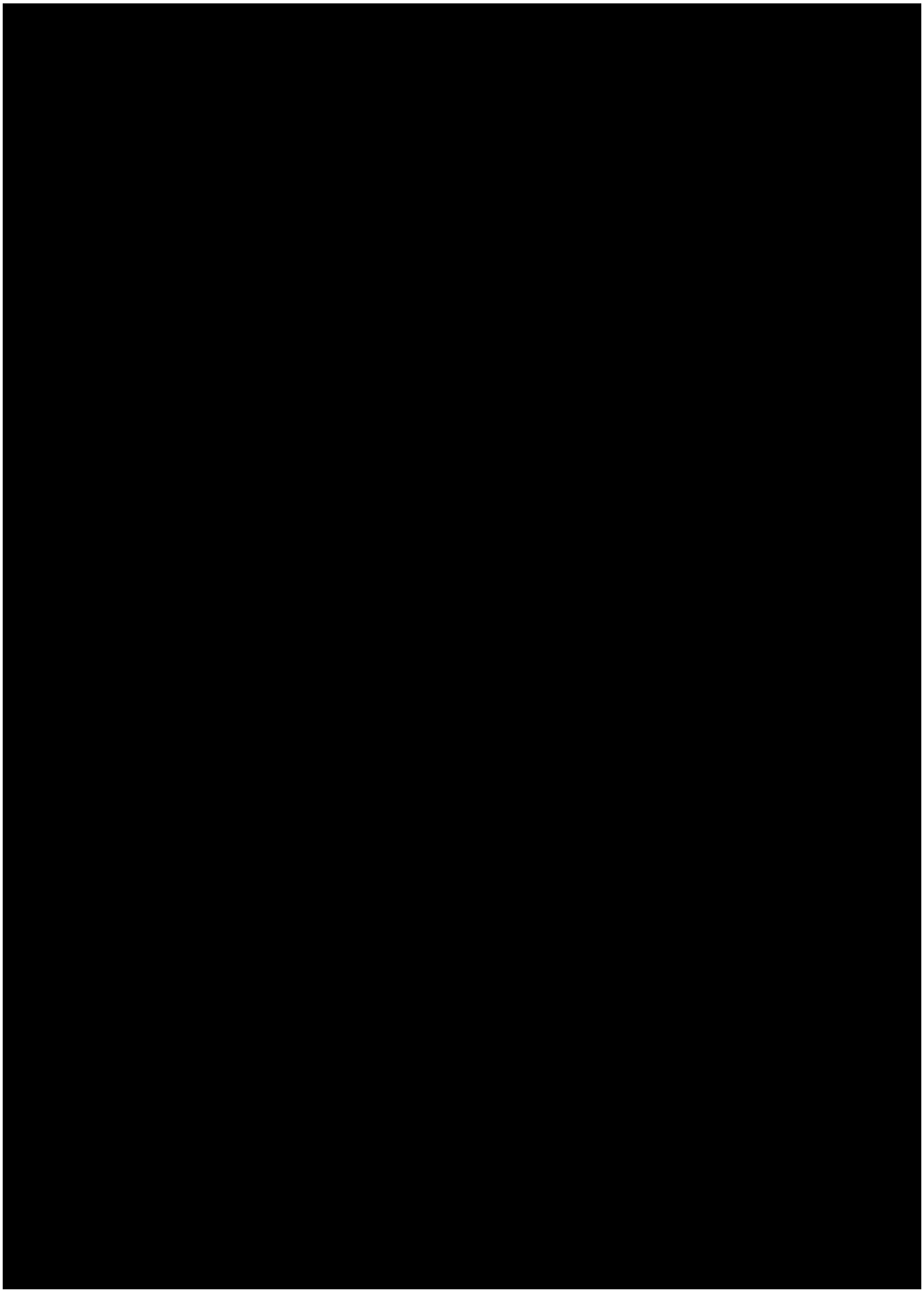
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

# APPENDIX G. CMP-001 INJECTION GUIDELINE

Syringe size is at the discretion of the Investigator or qualified designated staff for administering the CMP-001 study drug according to institutional guidelines or SOPs. Refer to the current Pharmacy Manual for additional information.

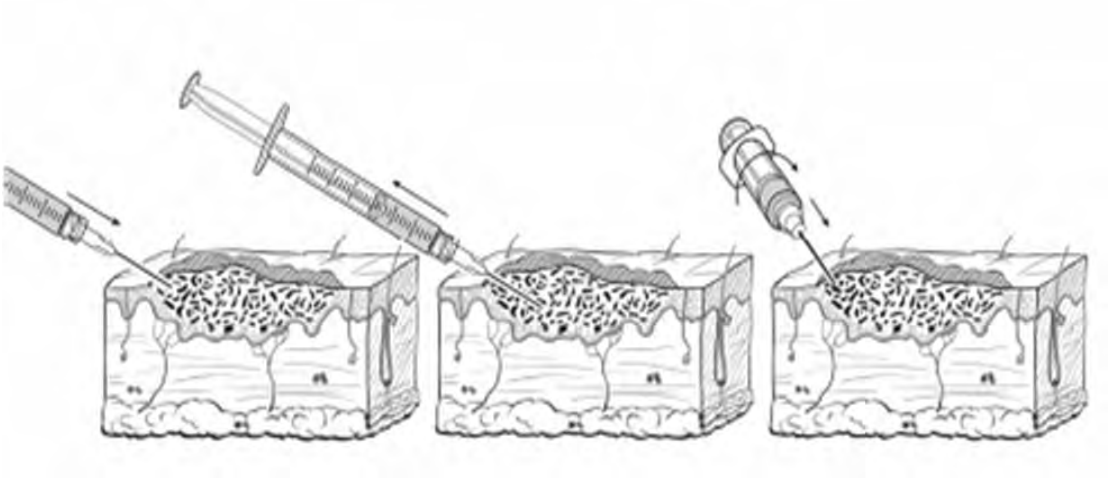
**Method of CMP-001 Administration**

**Intratumoral Injection**

Using standard aseptic technique, the needle should be inserted near the tumor periphery (Figure 4 left panel) and advanced into the tumor to the desired depth while maintaining gentle backward pressure on the syringe plunger to confirm an extravascular location of the needle tip. The syringe and needle should be slowly withdrawn to within a few millimeters of the skin or tumor surface while maintaining gentle downward pressure on the plunger to inject the desired volume of CMP-001 along the needle track (Figure 4 middle panel).

With the tip of the needle still under the skin, the syringe should be rotated by approximately 20 º to 40º and the process of insertion and injection during needle withdrawal repeated (Figure 4 right panel). Using this process, CMP-001 is injected IT along multiple tracks through a single insertion point as far as the radial reach of the needle allows within the tumor; 2 insertion points may be used if the tumor is larger than the radial reach of the needle or the intended volume cannot be delivered through a single insertion point. If gentle injection pressure along 5 needle tracks within the tumor has not succeeded in delivering the desired volume, then the remainder of the CMP-001 may be injected peritumorally around the same lesion. If the full volume cannot be injected within the tumor, the remaining drug volume should be injected into a second accessible tumor, if present; otherwise, the remaining volume should be injected SC near an original tumor (peritumoral).

**Figure 4: Method for CMP-001 Intratumoral Injection**



**Recommended Intratumoral Injection Volume Based on Lesion Size**

| Lesion Size (Longest Dimension) | CMP-001 Injection Volume |
|---|---|
| <0.5 cm | Up to 0.25 mL |
| 0.5 to 1.5 cm | Up to 0.5 mL |
| 1.5 to 2.5 cm | Up to 1 mL |
| >2.5 cm | 2 mL |

Note: If the full 2-mL dose cannot be accommodated within accessible tumor(s), then the remaining volume may be injected peritumorally.

**Subcutaneous Injection**

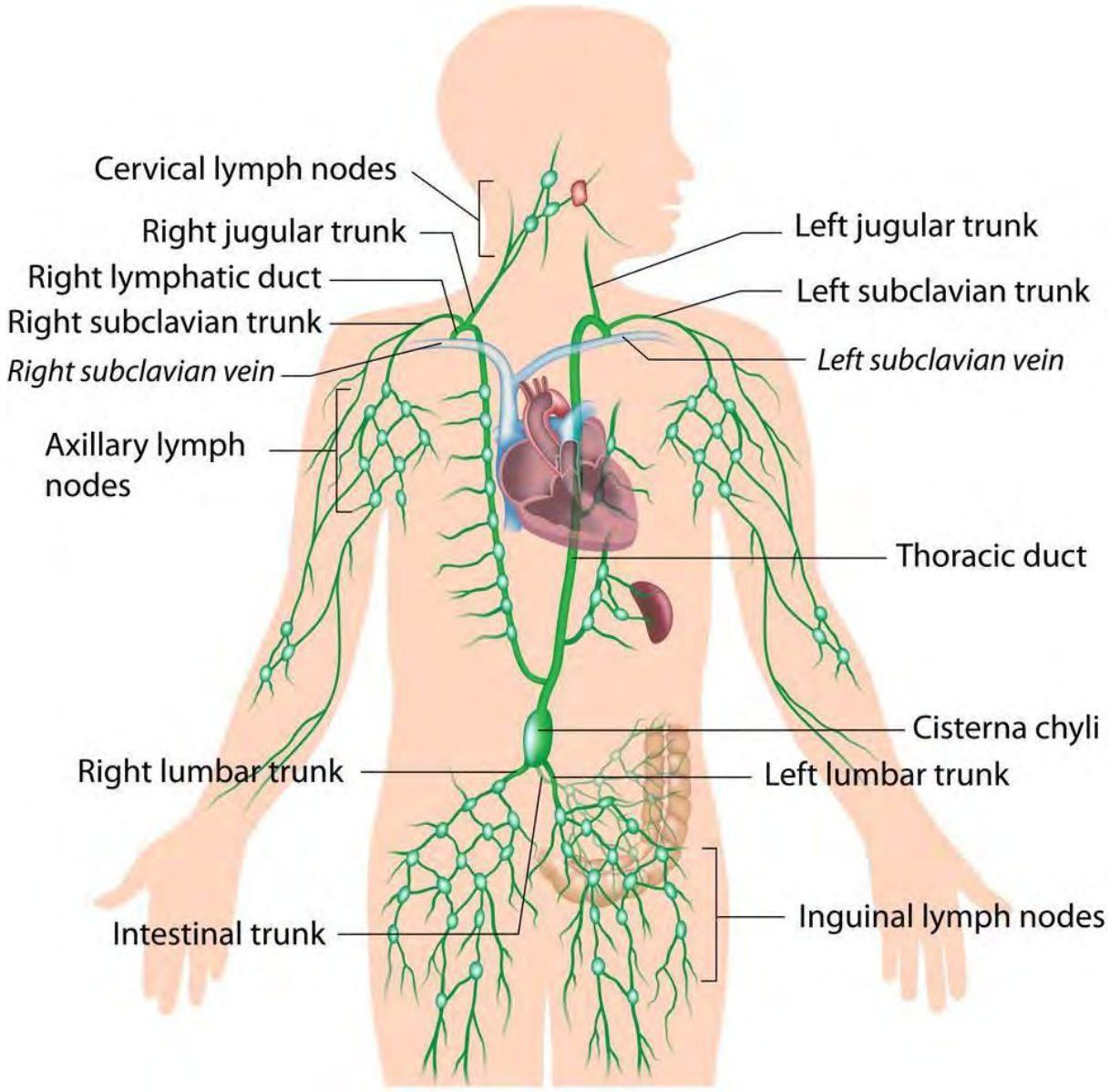
Subcutaneous administration of CMP-001 should only occur when all accessible lesions have regressed. CMP-001 SC can be administered within the area of lymphatic drainage corresponding to the site of metastatic disease and follow local standards for SC injection.

In order to maximize the distribution and exposure to CMP-001, the full volume from a single dose should be distributed to as many SC sites as is practical. It is recommended that equal amounts of drug be injected at each SC site.

Preferred sites of injection include the following:

- Location of the primary tumor.
- Within the area of lymphatic drainage corresponding to the site of metastatic disease. For example, in a subject with a muscle or bone metastasis in the lower leg, preferred SC injection sites would be in the same leg, with the expectation that at least some of the CMP-001 will drain to lymph nodes that also contain tumor antigens. Likewise, in a subject with metastases in an upper lobe of the lung, a preferred SC injection site would be in the ipsilateral supraclavicular fossa, where the injection may activate pDC in the supraclavicular lymph nodes that also can drain the upper lung.
- Unsuitable sites for injection would include, for example, the palm of the hand or the sole of the foot.

**Figure 5: Preferred Sites of Subcutaneous Injection**



# APPENDIX H. NIVOLUMAB SAFETY ALGORITHM

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

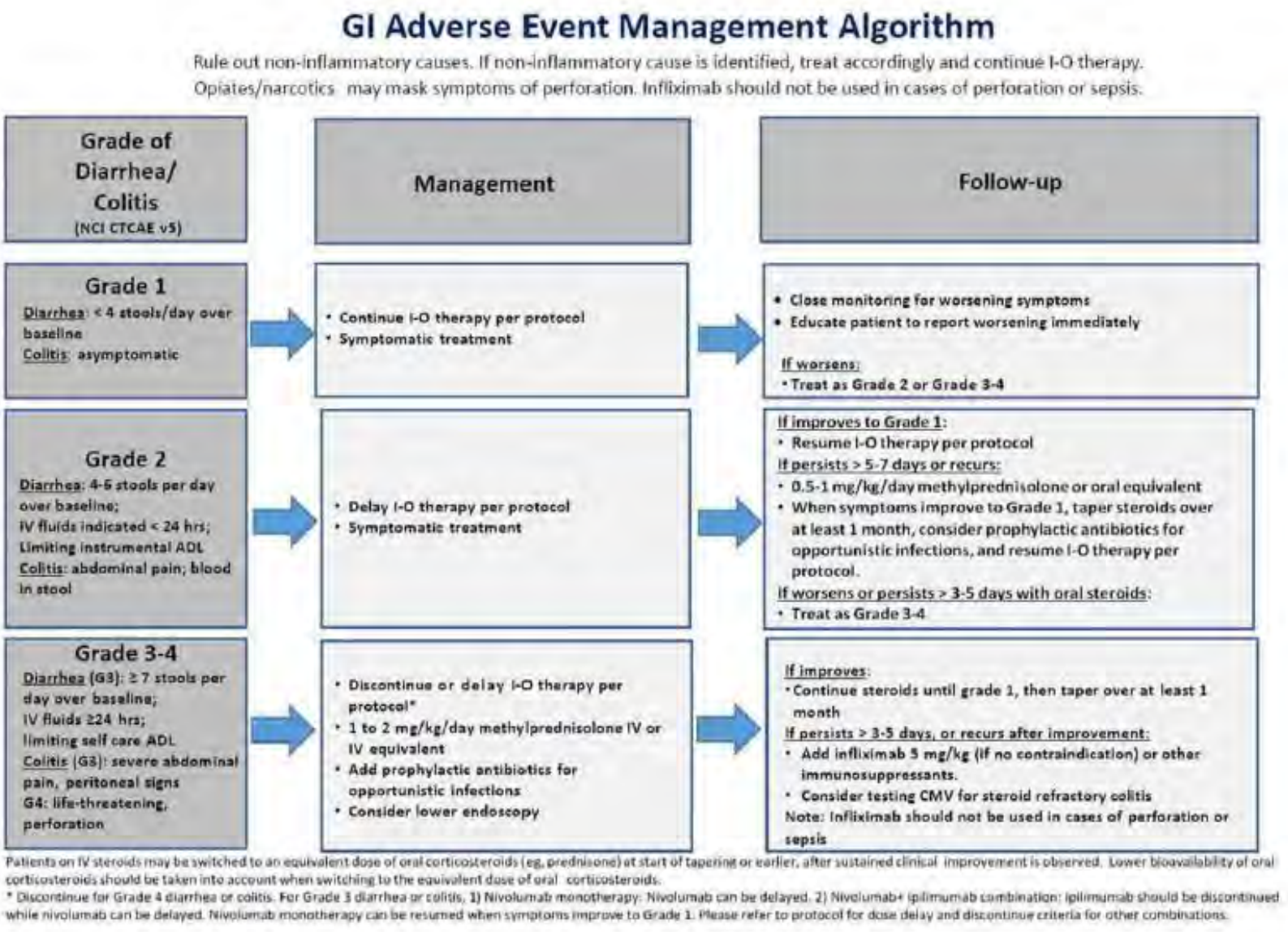
A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory subjects with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

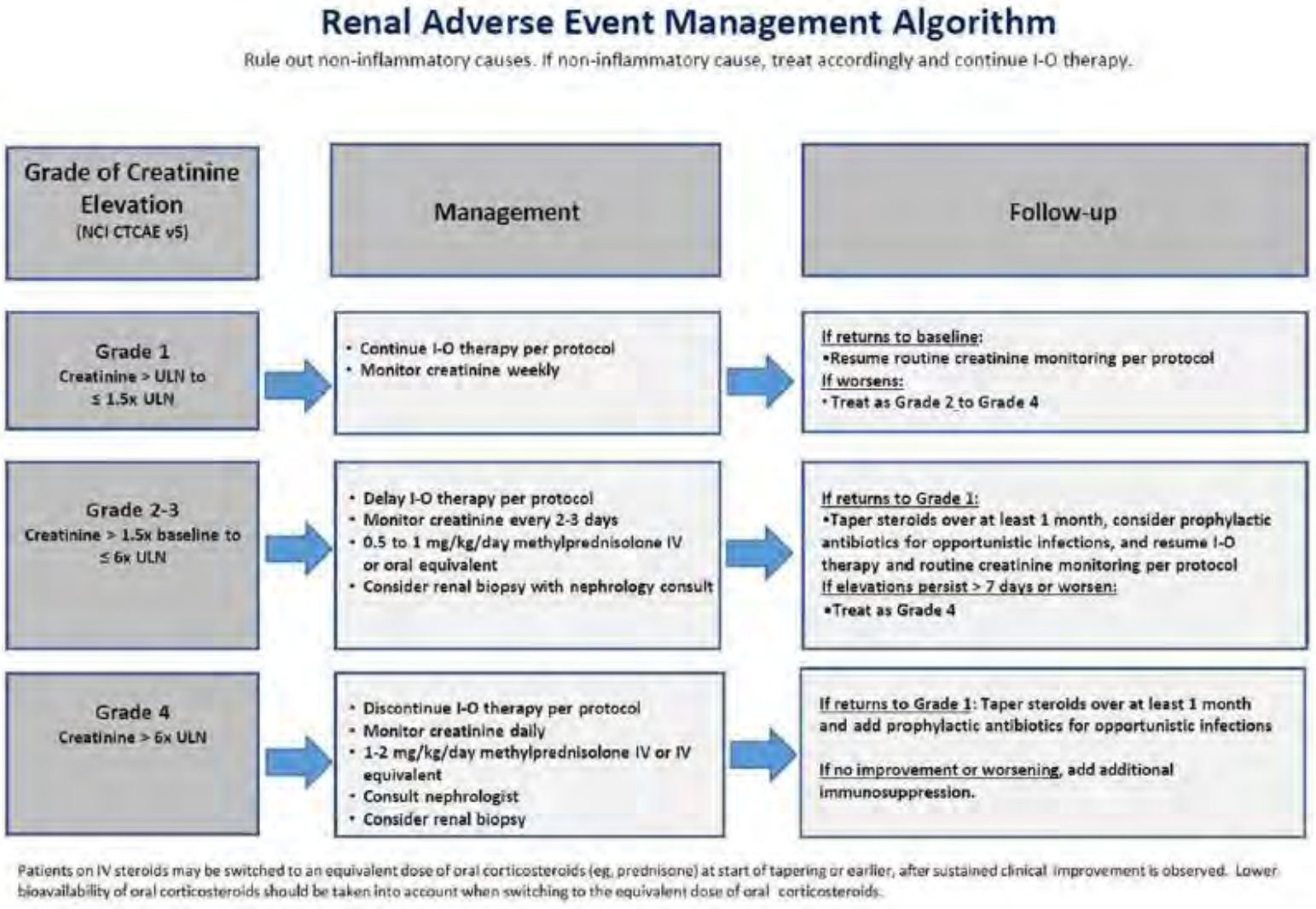
Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

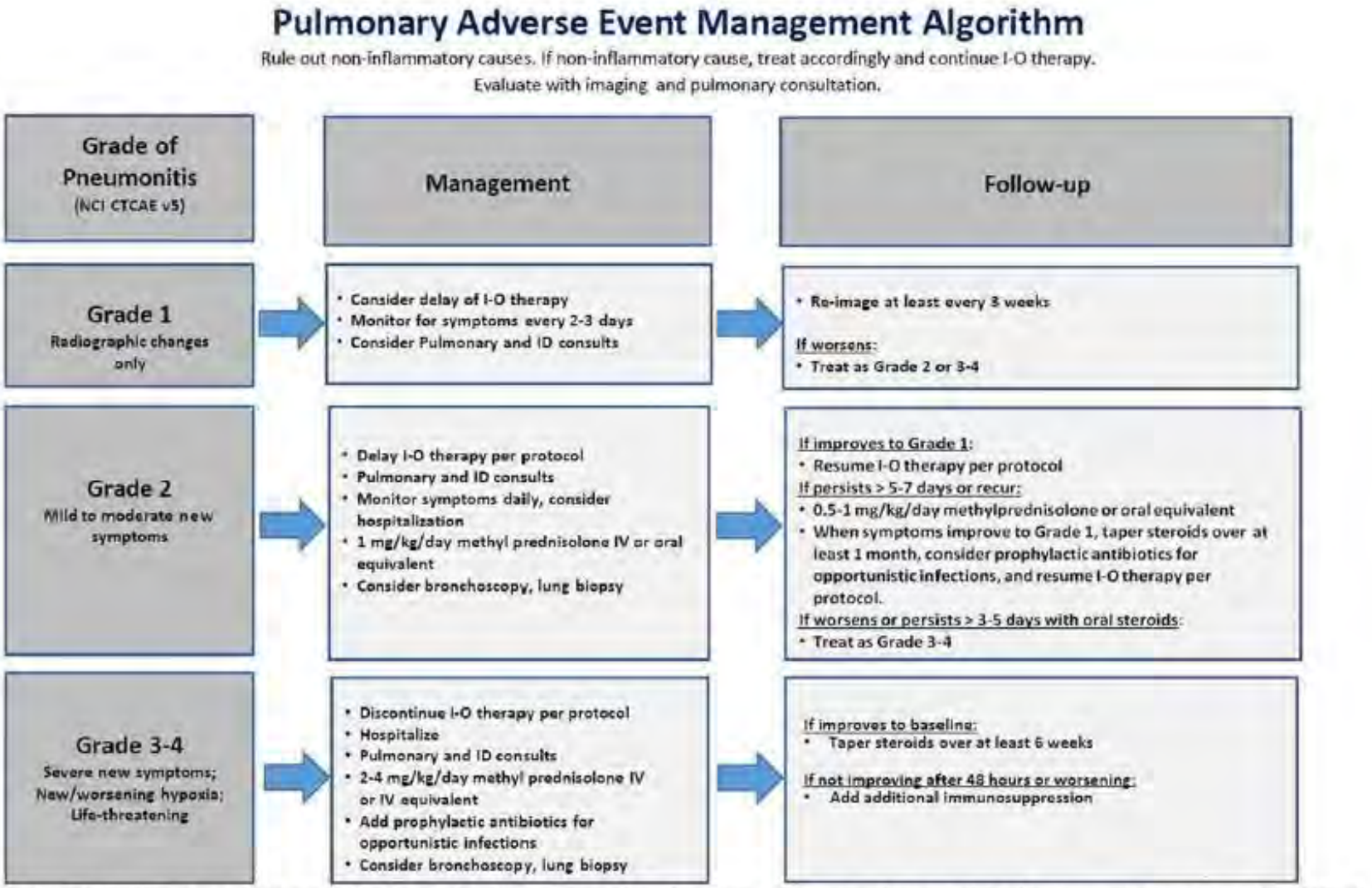
The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

**GI Adverse Event Management Algorithm**

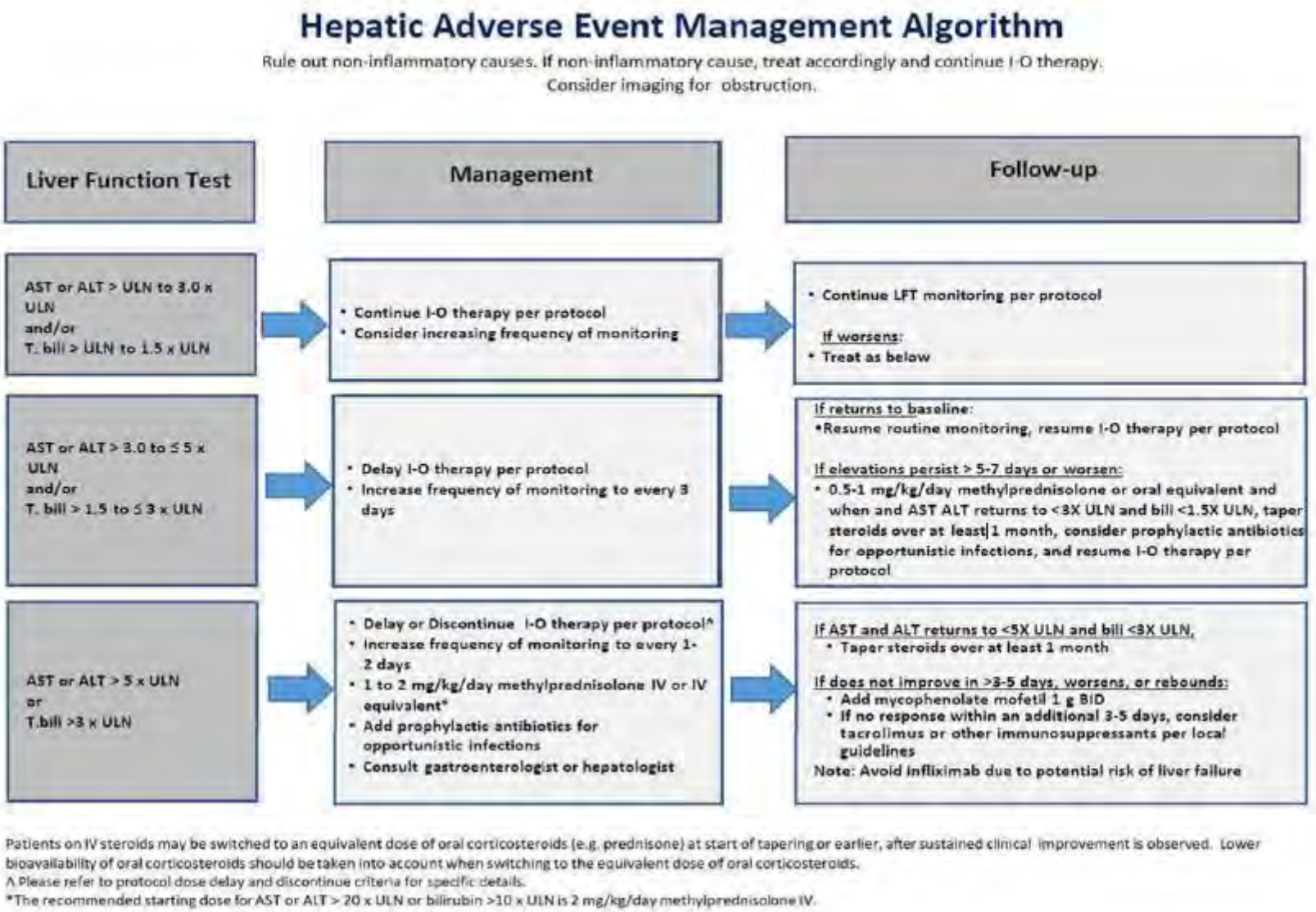


**Renal Adverse Event Management Algorithm**



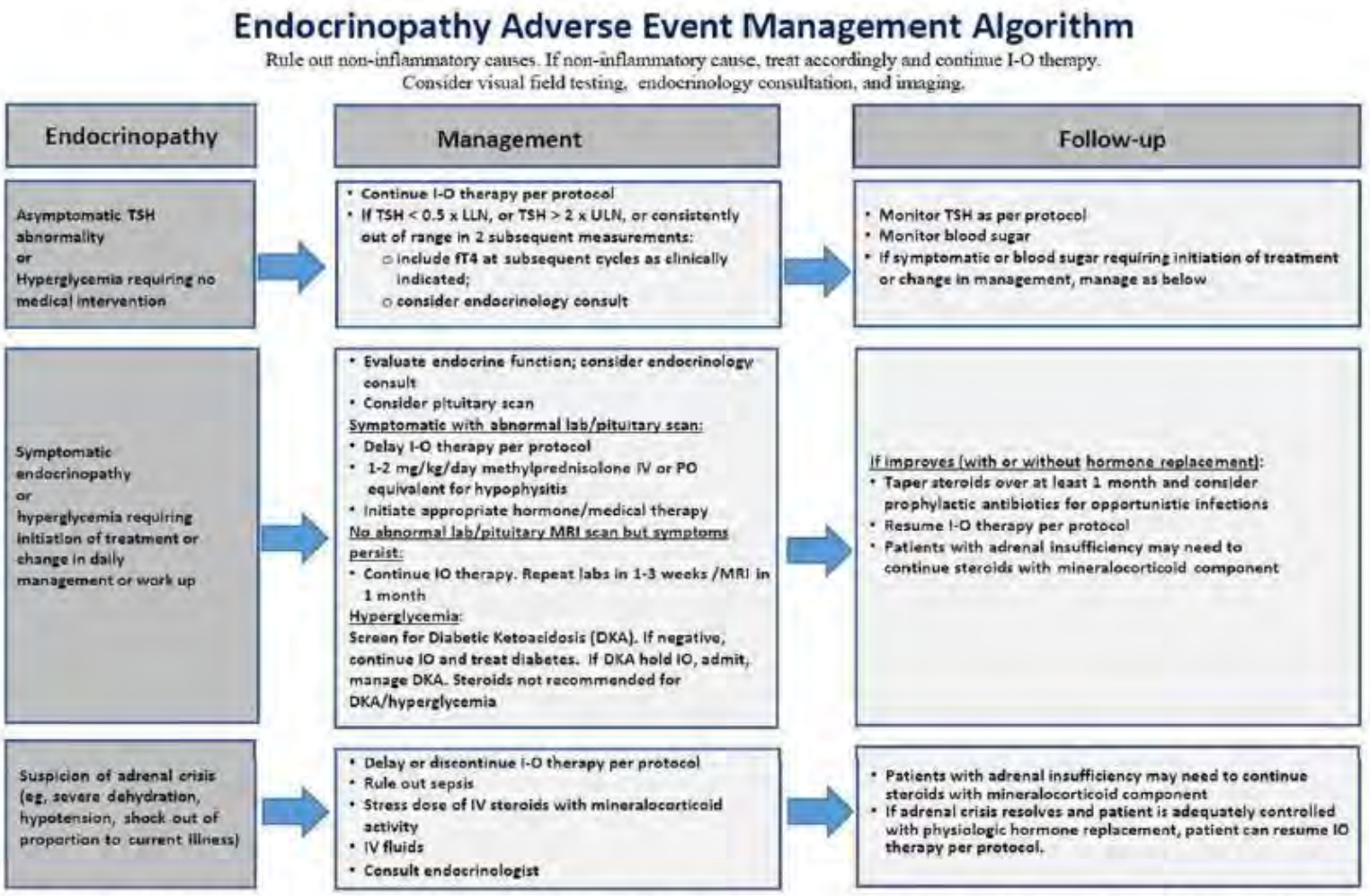


**Hepatic Adverse Event Management Algorithm**



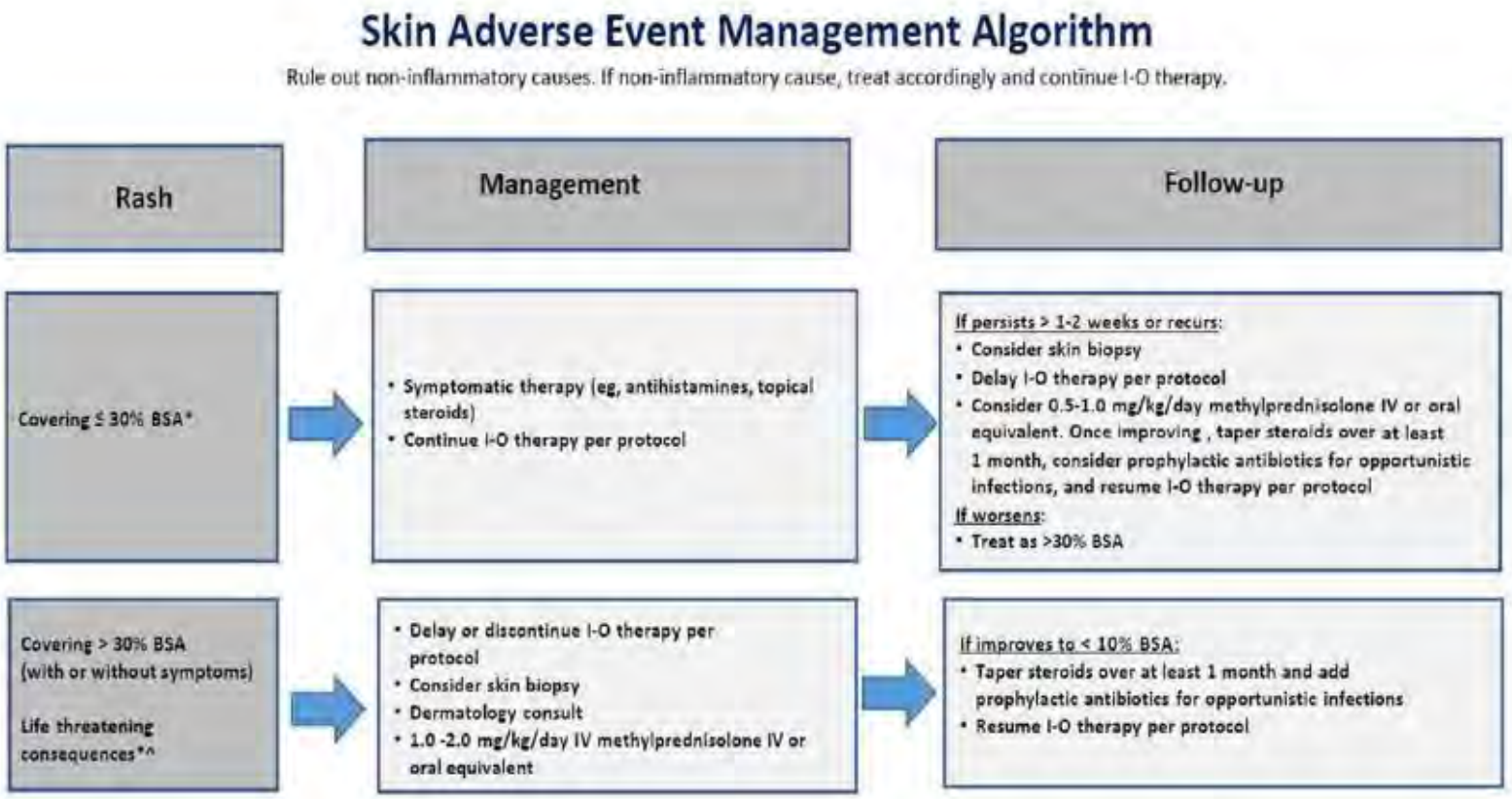

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
^ Please refer to protocol dose delay and discontinue criteria for specific details.
*The recommended starting dose for AST or ALT > 20 x ULN or bilirubin >10 x ULN is 2 mg/kg/day methylprednisolone IV.

## Endocrinopathy Adverse Event Management Algorithm




Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

**Skin Adverse Event Management Algorithm**

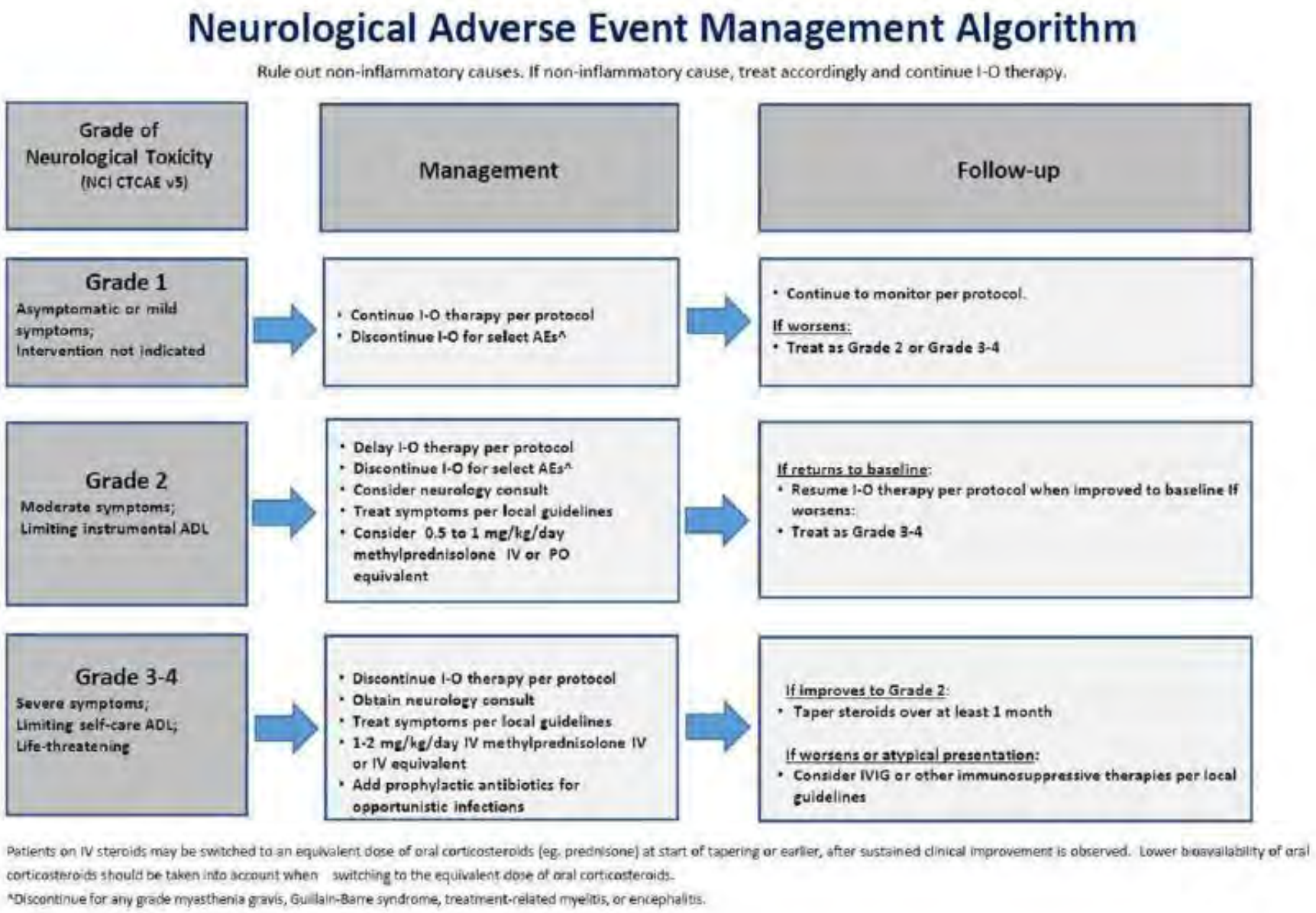



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*Refer to NCI CTCAE v5 for term-specific grading criteria.

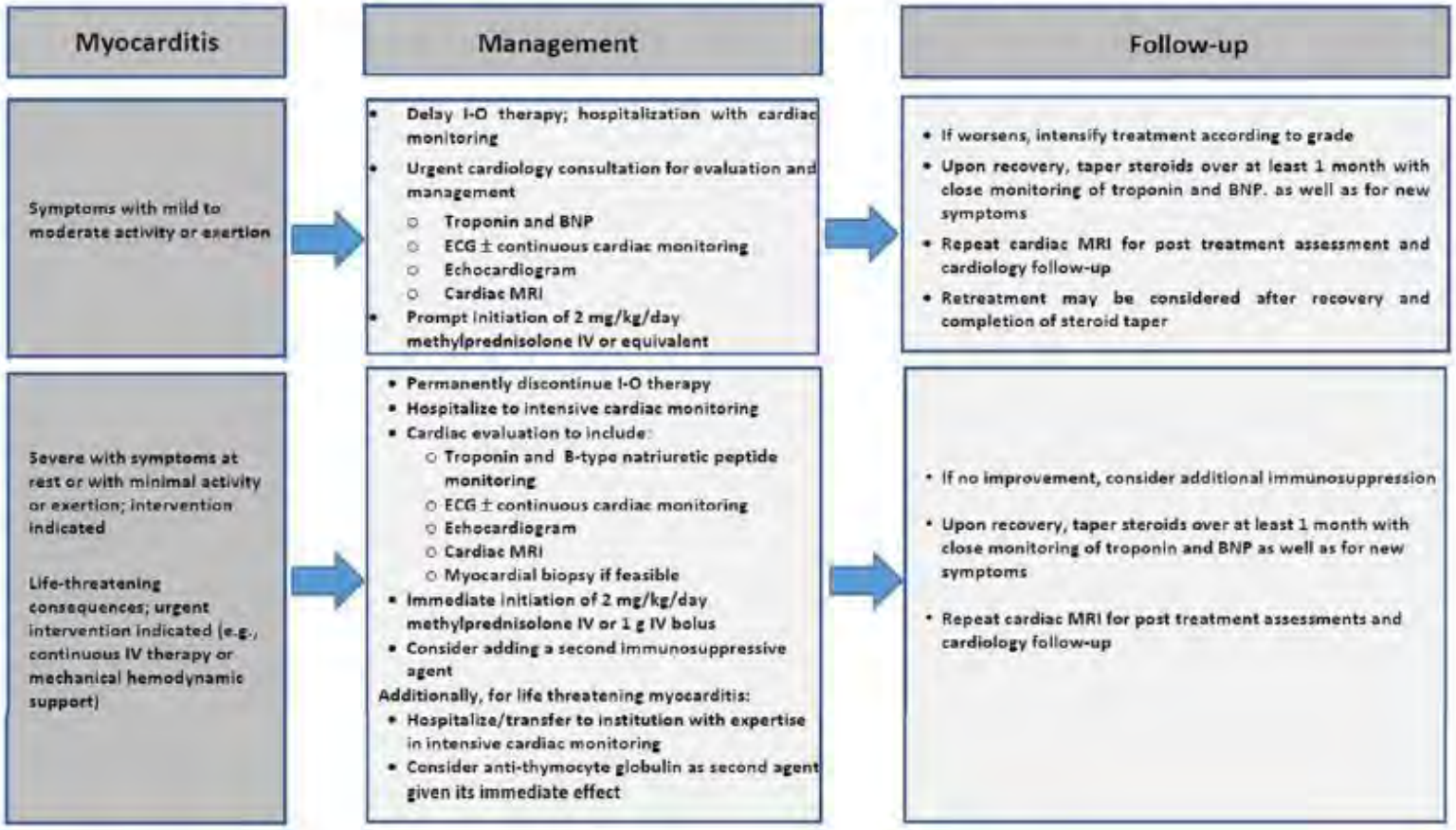
^If Steven-Johnson Syndrome (SJS),toxic epidermal necrosis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS, TEN, or DRESS is diagnosed, permanently discontinue I-O therapy.

**Neurological Adverse Event Management Algorithm**



# Myocarditis Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.




Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

# APPENDIX I. COUNTRY SPECIFIC REQUIREMENTS FOR HIV TESTING/EXCLUSION

Certain countries may require additional parameters for exclusion of HIV positive subjects which are local mandated.

As needed, the following table can be used to identify the changes needed to adapt the protocol to suit these local requirements.

| **Original Language** | **Country-Specific Language** |
|---|---|
| Section 4.1 Exclusion Criterion #16 | TBD |
| Section 7.1.12 Clinical Laboratory Assessments, Table 3 | TBD |
| Table 1, Schedule of Assessments | TBD |

# APPENDIX J. WOMEN OF CHILDBEARING POTENTIAL DEFINITION AND METHODS OF CONTRACEPTION

## DEFINITIONS

**Woman of Childbearing Potential (WOCBP)**

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

**Women in the following categories are not considered WOCBP**

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

## CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 5 months after the end of study treatment.*

| **Highly Effective Contraceptive Methods That Are User Dependent**<br>*Failure rate of <1% per year when used consistently and correctly.*[a] |
|---|
| • Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b]<br>– oral<br>– intravaginal<br>– transdermal |
| • Progestogen-only hormonal contraception associated with inhibition of ovulation[b]<br>– oral<br>– injectable |

| **Highly Effective Methods That Are User Independent** |
|---|
| • Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b]<br>• Intrauterine hormone-releasing system (IUS)[c]<br>• Intrauterine device (IUD)[c]<br>• Bilateral tubal occlusion |
| • Vasectomized partner<br>*A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.* |
| • Sexual abstinence<br>*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*<br>• It is not necessary to use any other method of contraception when complete abstinence is elected.<br>• WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2.<br>• Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence |
| NOTES:<br>[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.<br>[b] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.<br>[c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness |

| **Unacceptable Methods of Contraception*** |
|---|
| • Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously<br>• Diaphragm with spermicide<br>• Cervical cap with spermicide<br>• Vaginal Sponge with spermicide<br>• Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action |
| • Periodic abstinence (calendar, symptothermal, post-ovulation methods)<br>• Withdrawal (coitus interruptus).<br>• Spermicide only<br>• Lactation amenorrhea method (LAM) |

**Local laws and regulations may require use of alternative and/or additional contraception methods.**

## COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy is provided in Section 7.1.13 and Section 8.3.2.